OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

6

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: October 4, 2004

MEMORANDUM

SUBJECT: **Prothioconazole:** Screen of Submitted Studies for New Chemical.

FROM: Barry O'Keefe, Biologist
Registration Action Branch 3
Health Effects Division (7509C)

B. O'Keefe

THROUGH: Steve Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)

Stephen O-Dapson

TO: J. Tomerlin/D. McNeilly, PM Team 22
Registration Division (7505C)

PC Code: 113961 **DP Barcode:** D309007
Chemical: Prothioconazole

Action Requested:

New Chemical Screen of the toxicology, residue chemistry, and occupational exposure studies submitted for the registration of Prothioconazole on various agricultural crops; i.e., barley, wheat, rice, peanut, dry shelled pea and bean (except soybean) crop group, and oilseed (except sunflower and safflower) crop group.

HED Response:

The studies submitted to support the proposed uses of the new chemical, prothioconazole, have been screened for completeness and general acceptability. These studies have **passed the screen** and are eligible for complete reviews including hazard characterization and hazard identification for risk assessment. Please refer to the attached summation tables and screening criteria appendixes for specific details.

OCT 2 6 2004

Table 1. Toxicology Data Requirements (CFR 158.340) for the Food Use of Prothioconazole (JAU6476) and its Metabolite (SXX 0665).

Guideline No.	Study Type	Technical		
		Required	Submitted	MRID No.
870.3100	Subchronic (Oral) Toxicity - Rat	Y§	Y	46246309[d]
870.3100	Subchronic (Oral) Toxicity - Mouse			46246310[d]
870.3100	Subchronic (Oral) Toxicity - Rat			46246311[a]
870.3100	Subchronic (Oral) Toxicity - Rat			46246312[b]
870.3150	Subchronic (Oral) Toxicity - Dog	Y	Y	46246313[a]
				46246314[d]
870.3200	21/28-Day Dermal Toxicity - Rat	Y	Y	46246315[a]
870.3250	90-Day Dermal Toxicity	N		
870.3465	90-Day Inhalation Toxicity	N		
870.3700a	Prenatal Developmental (Oral) Toxicity -Rat	Y¶	Y	46246316[a]
				46246321[d]
870.3700a	Prenatal Developmental (Dermal) Tox -Rat			46246323[a]
870.3700a	Prenatal Developmental (Oral) Toxicity -Rat			46246324[b]
870.3700a	Prenatal Developmental (Dermal) Tox -Rat			46246325[d]
870.3700b	Prenatal Developmental (Oral)Tox - Rabbit	Y	Y	46246327[d]
				46246328[a]
870.3800	Reproduction and Fertility Effects	Y	Y	46246333[d]
				46246334[a]
870.4100a	Chronic (Oral) Toxicity - Rat-	Y	Y	46246335[a]
870.4100b	Chronic (Oral) Toxicity - Dog	Y	Y	46246336[a]
				46246337[d]
870.4200a	Carcinogenicity -Rat	Y	Y	46246338[a]
870.4200b	Carcinogenicity - Mouse	Y	Y	46246339[a]
				46246340[d]
870.4300	Combined Chronic Toxicity /Carcinogenicity (mouse)	Y	Y	46246342[d]
870.6100a	Neurotoxicity - Acute Delayed Neurotox.- Hen	N		
870.6100b	Neurotoxicity - Subchronic - Hen	N		
870.6200a	Neurotoxicity Screening Battery - Acute - Rat	Y	Y	46246417[a]
870.6200b	Neurotoxicity Screening Battery - Subchronic - Rat	Y	Y	46246416[a]
870.6300	Developmental Neurotoxicity - Rat	Y	Y	46246418[d]

§ Required in rodent and non-rodent
¶ Required in rat and rabbit
a JAU 6476
b JAU 6476 Sulfonic Acid K Salt
c JAU 6476 des chloro
d SXX 0665

Table 2. Toxicology Data Requirements Screening Results

New Guideline	Old Guideline	Guideline Description	Study Title	MRID	Screening Decision	Comments
870.3100	82-1(a)	Subchronic Oral Tox - Rodent	SL-160 Technical: 13-Week Oral Subchronic Toxicity in Rats.	46220920	Acceptable for Review	
870.3150	82-1(b)	Subchronic Oral Tox - Non-Rodent	AL-160 Technical: 13-Week Oral Subchronic Toxicity in Dogs.	46220921	Acceptable for Review	
870.3200	82-2	21/28 Day Dermal Toxicity	A 21-Day Repeated Dose Dermal Toxicity Study in Albino Rabbits with Technical SL-160.	46220922	Acceptable for Review	
870.3700	83-3(a)	Prenatal Developmental Toxicity - Rodent	Teratology Study in Rats with SL-160 Technical	46220924	Acceptable for Review	No historical data
			Technical: Developmental Toxicity Study in Rats	46220925	Acceptable for Review	
870.3700	83-3(b)	Prenatal Developmental Toxicity - Non-Rodent	Teratology Study in Rabbits with SL-160 Technical	46220923	Acceptable for Review	No historical data; Only 17 pregnancies
870.3800	83-4	Reproduction & Fertility Effects	A Two Generation Reproduction Study in Rats with Technical SL-160	46220926	Acceptable for Review	Minor deficiencies
870.4100	83-1(b)	Chronic Oral Toxicity - Non-Rodent	SL-Technical: 12-Month Oral Chronic Toxicity Study in Dogs	46220927	Acceptable for Review	
870.4200	83-2(b)	Carcinogenicity - Mouse	An Oncogenicity Study in Mice with SL-160	46220928	Acceptable for Review	No purity; No neoplasm, same batch as other studies
870.4300	83-5	Combined Chronic Toxicity/Carcinogenicity	SL-Technical: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats	46220929	Acceptable for Review	No neoplasms at toxic lethals
870.5100	84-2	Ames	SL-160 Technical: Microbial Mutagenicity Study	46220933	Acceptable for Review	Negative up to cytotox; no historical control data
870.5300	84-2	In-vitro Mammalian Cell Gene Mutation test	L5178Y TK +/- Mouse Lymphoma Mutagensis Assay with Confirmatory Assay with SL-160	46220930	Acceptable for Review	Negative up to precipitation

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New Guideline	Old Guideline	Guideline Description	Study Title	MRID	Screening Decision	Comments
870.5375	84-2	In-vitro Mammalian Chromosome Aberration test	SL-160 Technical: In-Vitro Cytogenics Test	46220931	Acceptable for Review	Negative up to growth inhibition
870.5395	84-2	Mammalian Erythrocyte *Micronucleus test*	Micronucleus Cytogenic Assay in Mice *with SL-160*	46220932	Acceptable for Review	Negative; No historical control data
870.6200	81-8	Neurotoxicity Screening	An Acute Neurotoxicity Screening Study in Rats with SL-160	46220934	Acceptable for Review	No positive control data
[illegible]	[illegible]	[illegible] Pharmacokinetics	*Study to Identify and Characterize the* Metabolites of (Carbon 14)-SL-160	46220935	Acceptable for Review	
			Study of the Biliary Excretion of Radiolabel Following Oral Administration of (Carbon 14)-SL-160(P) to Sprague-Dawley Rats	46220936	Acceptable for Review	
			Study of the Biliary Excretion of Radiolabel Following Oral Administration of (Carbon 14)-SL-160(Pm) to Sprague-Dawley Rats	46220937	Acceptable for Review	
			Study to Evaluate the Distribution and Excretion of (Carbon 14)-SL-160(P) in Rats	46220938	Acceptable for Review	
			Study to Evaluate the Distribution and Excretion of (Carbon 14)-SL-160(Pm) in Rats	46220939	Acceptable for Review	
			Study to Evaluate the Distribution and Excretion of (Carbon 14)-SL-160 in Rats	46220940	Acceptable for Review	
			Study to Evaluate the Distribution and Excretion of (Carbon 14)-SL-160(Pm) Following Repeated Administration of SL-160 in Rats	46220941	Acceptable for Review	

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New Guideline	Old Guideline	Guideline Description	Study Title	MRID	Screening Decision	Comments
			Study to Evaluate the Pharmacokinetics of (Carbon 14)-SL-160(P) in Blood of Rats	46220942	Acceptable for Review	
			Study to Evaluate the Pharmacokinetics of (Carbon 14)-SL-160(Pm) in Blood of Rats	46220943	Acceptable for Review	

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Table 3. Residue Chemistry Data Requirements Screening Results

Food X (Rice, barley, peanuts, canola and wheat) Non-Food _____

Title of study	OPPTS Guideline No.	Received	Comments
Product chemistry:			
Directions for use	860.120(	Y	Acceptable The Section B and label for prothioconazole Technical and the formulated product Proline® 480 SC Fungicide has been submitted.
Nature of residue - plant [wheat, peanuts & sugar beets]	860.130(	Y	Acceptable MRID 46246241-48
Nature of residue - ruminant [Lactating Goat]	860.130)	Y	Acceptable MRID 462462-01, 462462-49 & 462462-50
Nature of residue - poultry [Laying Hens]	860.130)	Y	Acceptable MRID 46246202 &46246203
Residue analytical method - plants	860.134)	Y	Acceptable MRID 46246206 & 46246208
Residue analytical method - plants (ILV)	860.134)	Y	Acceptable MRID 46246209
Residue analytical method - livestock	860.134)	Y	Acceptable MRID 46246204 &46246205
Residue analytical method - livestock (ILV)	860.13(0	Y	Acceptable MRID 46246207
Multi-residue method	860.13(0	Y	MRID 46246210

Title of study	OPPTS Guideline No.	Received	Comments
Storage stability data in crops	860.1380	Y	Acceptable MRID 46246211
Storage stability data in soil	860.1380	NA*	
Water, fish, & irrigated crops	860.1400	NA	
Water, fish, & irrigated crops	860.1400	NA	
Food handling	860.1460	NA	
Meat/milk/poultry/eggs ruminant	860.1480	Y	Acceptable MRID 46246213 &46246214
Meat/milk/poultry/eggs poultry	860.1480	N	The petitioner has submitted a waiver request for poultry feeding study. The waiver is acceptable. However, tolerance on poultry liver may be needed.
Crop field trails for [Rice]	860.1500	Y	Acceptable MRID 462462-16 The petitioner should submit residue data for crawfish or change label to restrict fish farming.
Crop field trails for [Peanuts]	860.1500	Y	Acceptable MRID 462462-29
Crop field trails for [Dried peas & beans (crop subgroup 6C]	860.1500	Y	Acceptable MRID 462462-21
Crop field trails for [Barley]	860.1500	Y	Acceptable MRID 462462-20
Crop field trails for [Canola]	860.1500	Y	Acceptable MRID 462462-15

Title of study	OPPTS Guideline No.	Received	Comments
Crop field trails for [Wheat]	860.1500	Y	Acceptable MRID 462462-19
Process food/feed for [Rice]	860.152(	Y	Acceptable MRID 462462-22
Process food/feed for [Canola]	860.152(	Y	Acceptable MRID 462462-24
Process food/feed for [Peanuts]	860.152(	Y	Acceptable MRID 462462-23
Process food/feed for [Wheat]	860.152(	Y	Acceptable MRID 462462-18
Process food/feed for [Barley]	860.152(	N	Based on OPPTS 860.1520, wheat processing study can be translated to barley.
Confined accum. in rotational crops	860.185(	Y	Acceptable MRID 462462-25 & 462462-26
Field accum. in rotational crops	860.190(	Y	Acceptable MRID 462462-27

*Not applicable

Table 4. Occupational Exposure Data Requirements Screening Results

Title of study	OPPTS Guideline No.	Received	Comments
Mixer/Loader/Applicator Exposure Monitoring Study	875.1500	MRID 46246447	Acceptable for review
Registrant's Occupational Exposure & Safety Assessment	875.0000	MRID 46246446	No comment
Summaries for Occupational & Residential Exposure Studies	---	MRID 46246448	No comment

Appendix 1. Bibliography of the S ubmitted Toxicology Studies

159
Schladt, L. (1999). SXX 0665 Study on Subchronic Toxicity in Wistar Rats (Diet ry Administration Over 14 Weeks with a Subsequent Recovery Period Over 5 Weeks). 545 pages. Bayer Report No. 109446.
870.3100 **46246309**

160
Wirnitzer, U. (1999). SXX 0665 Dose Range-Finding Study in B6C3F1 Mice (Dietary Administration for About 13 Weeks) (with Amendment Attached). 33 5 pages. Bayer Report No. 109445 &1094 45-1.
870.3100 **46246310**

161
Wirnitzer, U. (1999). JAU 6476 Study oı Subchronic Toxicity in Wistar Rats (Administration by Gavage Over 14 We ks with a Subsequent Recovery Period of Weeks). 559 pages. Bayer Report No. 109095.
870.3100 **46246311**

162
Andrews, P. (2001). JAU 6476-Sulfonic Acid K-Salt Study for Subchronic Oral Toxicity in Rats (Feeding Study for 13 Weeks). 371 pages. Bayer Report No. 31441.
870.3100 **46246312**

163
Jones, R. (2001). Technical Grade JAU 6476 A Subchronic Oral Gavage Study in the Beagle Dog. 1314 pages. Bayer Re ort No. 109442.
870.3150 **46246313**

164
Hoffmann, W. (2000). SXX 0665 *Subchronic Toxicity Study in Beagle D gs* (13 Week Feeding Study). 360 pages. Bayer Report No. 29616.
870.3150 **46246314**

165
Krotlinger, K. Krotlinger, K. (2000). JAU 6476 Study for Subacute Dermal Toxicityin Rats (Four-Week Treatment Period). 227 pages. Bayer Report No. 30115.
870.3200 **46246315**

166
Stahl, B. (1996). JAU 6476 Developmental Toxicity Study in Rats after Oral Administration. 671 pages. Bayer Report No. 109074.
870.3700 **46246316**

167
Klaus, A. (2002). JAU 6476-Des-Chloro Pilot Developmental Toxicity Study in Rats After Oral Administration. 228 pages. Bayer Report No. AT00172.
870.3700 **46246317**

168
Becker, H. (2001). JAU 6476-Sulfonic Acid K. Salt Dose Range-Finding Study to a Prenatal Developmental Toxicity Study in the Rat. 153 pages. Bayer Report No. R7936.
870.3700 **46246318**

169
Holzum, B. (1992). SXX 0665 Embryotoxicity Study on Postnatal Development of Supernumerary Ribs in Rats Following Oral Administration. 177 pages. Bayer Report No. 109269.
870.3700 **46246319**

170
Renhof, M. (1990). SXX 0665 Exploratory Study for Embryotoxic Effects in Rats Following Oral Administration. 131 pages. Bayer Report No. 18661.
870.3700 **46246320**

171
Becker, H. (1991). Embryotoxicity Study (Including Teratogenicity) with SXX 0665 Technical in the Rat. 324 pages. Bayer Report No. 108979.
870.3700 **46246321**

172
Becker, H. (1991). Supplementary Study to the Embryotoxicity Study (Including Teratogenicity) with SXX 0665 Technical in the Rat. 193 pages. Bayer Report No. 108979-1.
870.3700 **46246322**

173
Young, A. (2001). A Dermal Developmental Toxicity Study with (JAU 6476, Technical Material and Products) in the Wistar Rat. 521 pages. Bayer Report No. 108993.
870.3700 **46246323**

174
Becker, H. (2001). JAU 6476-Sulfonic Acid K.Salt Prenatal Developmental toxicity Study in the Rat. 275 pages. Bayer Report No. R7997.
870.3700 **46246324**

175
Holzum, B. (1991). SXX 0665 Study for Embryotoxic Effects in Rats Following Dermal Exposure. 232 pages. Bayer Report No. 109280.
870.3700 **46246325**

176
Bartmann, K. (1991). SXX 0665 Supplementary Study for Embryotoxic Effects in Rats Following Dermal Exposure. 178 pages. Bayer Report No. 109280-1
870.3700 **46246326**

177
Bartmann, K. (1991). SXX 0665 Study for Embryotox Effects in Rabbits Following Oral AdministrationSXX 0665 Study for Embryotox Effects in Rabbits Following Oral Administration. 191 pages. Bayer Report No. 109270.
870.3700 **46246327**

178
Becker, K. (1998). Developmental Toxicity Study with JAU 6476 in the Rabbit. 369 pages. Bayer Report No. 108657.
870.3700 **46246328**

179
Becker, K. (1991). Dose Range-Finding Embryotoxicity Study (Including Teratogenicity) with SXX 0665 Technical in the Rabbit (Dermal Application). 92 pages. Bayer Report R5425.
870.3700 **46246329**

180
Becker, K. (1997). Dose Toleration Study to a Developmental Toxicity Study with JAU 6476 in the Rabbit. 112 pages. Bayer Report No. R7003.
870.3700 **46246330**

181
Astroff, A. (1999). A Pilot Reproductive Toxicity Study with JAU 6476 Technical in the Wistar Rat. 306 pages. Bayer Report No. 109079.
870.3800 **46246331**

182
Eigenberg, D. (1992). Pilot Study to Establish Dose Levels for a Two-Generation Reproduction Study in Rats Using Technical Grade SXX 0665 Administered via the Diet. 232 pages. Bayer Report No. 103274.
870.3800 **46246332**

183
Eigenberg, D. (2001). A Two-Generation Dietary Reproduction Study in Rats Using SXX 0665. 959 pages. Bayer Report No. 109835.
870.3800 **46246333**

184
Young, A. (2001). A Two-Generation Reproductive Toxicity Study with JAU 6476 in the Wistar Rat. 1441 pages. Bayer Report No. 110500.

870.3800 **46246334**

185
Wirnitzer, U. (2000). JAU 6476 Study on Chronic Toxicity in Wistar Rats (Administration via Gavage Over 1 Year . 751 pages. Bayer Report No. 30536.
870.4100 **46246335**

186
Jones, R. (2001). Technical Grade JAU 6476 A Chronic Oral Gavage Study in th e Beagle Dog. 980 pages. Bayer Report N o. 110921.
870.4100 **46246336**

187
Henninger, K. (2001). SXX 0665 Chroni : Toxicity Study in Beagle Dogs (30 Weel Feeding Study). 525 pages. Bayer Repc rt No. 31148.
870.4100 46246337

188
Wirnitzer, U. (2001). JAU 6476 Study o Carcinogenicity in Wistar Rats (Adminsitration via Gavage Over 2 Yea s). 1780 pages. Bayer Report No. 31512.
870.4200 **46246338**

189
Schladt, L. (2001). JAU 6476 Oncogen city Study in CD-1 Mice (Administratition vi Gavage for 18 Months). 1396 pages. Bayer Report No. 31510.
870.4200 **46246339**

190
Wirnitzer, U. (2000). SXX 0665 Oncogenicity Study in B6C3F1-Mice (Dietary Administration via Gavage for 18 Months). 1326 pages. Bayer Report Nc . 30045.
870.4200 **46246340**

191
Wirnitzer, U. (2000). SXX 0665 Oncogenicity Study in B6C3F1-Mice (Dietary Administration via Gavage for 18 Months) Supplemental Submission. 13 pages. Bayer Report No. 30045-1.
870.4200 **46246341**

192
Schladt, L. (1999). SXX 0665 Combined Study on Chronic Toxicity and Carcinogenicity in Wistar Rats (Dietary Administration Over 2 Years). 1854 pages. Bayer Report No. 109447.
870.4300 **46246342**

216
Sheets, L. (2001). A Subchronic Oral Neurotoxicity Screening Study with Technical Grade JAU 6476 in Wistar Rats. 482 pages. Bayer Report No. 109968.
870.6200 **46246416**

217
Sheets, L. (2000). An Acute Oral Neurotoxicity Screening Study with Technical Grade JAU 6476 in Wistar Rats. 439 pages. Bayer Report No. 109250.
870.6200 **46246417**

218
Sheets, L.P., Lake, S.G. (2004). A Developmental Neurotoxicity Screening Study with Technical Grade SXX0665 in Wistar Rats. 1111 pages. Bayer Report No. 200958.
870.6300 **46246418**

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246309

870.3100 Subchro ıic 90-Day Oral Toxicity in Rodents - Rat - Diet

Does this study meet the following ıcceptance criteria?

No.	Yes/No	Criteria
1	**Y**	Study condu ted under GLP (with statement).
2	**Y**	Technical fo m of the active ingredient used
3	**Y**	Full identifi ation of the test material (physical state, color, batch or lot number, expiration d te, percentage active).
4	**Y**	Rat is prefe red species, although other rodent species can be used.
5	**Y**	Identificatio ı as to test animal strain and source.
6	**Y**	Testing start d with young healthy animals, no older than 8-9 weeks old for rats.
7	**Y**	At least 10 a ıimals/sex/dose level, with concurrent control group.
8	**NA**	If interim sa rifices, number of animals/group should be increased accordingly.
9	**Y**	Dosing dura ion of 90 days or 5 days/week for 13 weeks. **DIETARY**
10	**Y**	Doses teste include a NOAEL[1]
11	**Y**	Highest dos level produces indications of toxicity or is a limit dose (1000 mg/kg)
12	**Y**	Analyses fo test material stability, homogeneity and concentration in dosing medium.
13	**Y**	Individual d ily observations.
14	**Y**	Individual b ody weights (before administration, weekly thereafter, and at death).
15	**Y**	Individual c r cage food consumption.
16	**Y**	Ophthalmo copic examination (pretest & term) for at least control and high dose.
17	**N**	Assessmen of motor activity, grip strength, reactivity to sensory stimuli (not earlier than week 11).

[1]Does selected based on the results of a 28-day [MRID No. 46246430] & a 25-day [MRID No.] feeding stu lies in rats & the combination rat [MRID 46246342]. Study initiation: 12-10-92. Combina ion rat study initiation: 10-31-90.

18	**Y**	Hematology and clinical chemistry at termination.
19	**Y**	**Hematology** __X__ Erythrocyte count __X__ Leukocyte count __X__ Differential count __X__ Hemoglobin __X__ Hematocrit __X__ Mean corpuscular volume __X__ Mean corpuscular hemoglobin __X__ Mean corpuscular hemoglobin concentration __X__ Platelet count __X__ Prothrombin time or activated partial thromboplastin time
20	**Y**	**Clinical Chemistry** __X__ Potassium __X__ Urea nitrogen __T3/T4__ Triglycerides __X__ Sodium __X__ Creatinine __X__ Alanine aminotransferase __X__ Aspartate aminotransferase __X__ Alkaline phosphatase __X__ Glucose __X__ Total protein __X__ Albumin __X__ Total cholesterol _____ Cholinesterases (if appropriate.)
21[1]	**Y**	**Urinalysis** (optional; during last week: parameters include: __X__ appearance, __X__ volume, __X__ osmolality or specific gravity, __X__ pH, __X__ protein, __X__ glucose, and __X__ blood or blood cells.
22	**Y**	Individual gross necropsy of all animals
23	**Y**	**Organ weights:** __X__ Liver __X__ Ovaries __X__ Spleen __X__ Kidneys _____ Uterus __X__ Brain __X__ Adrenals _____ Thymus __X__ Heart __X__ Testes (with Epididymides)
24	Y	Full histopathology of the following tissues from at least all control and high-dose animals, and all rodents that died or were killed during the study, all gross lesions in all animals, and target tissues in all animals.

25	Y	X	adrenals	X	jejunum	X	pituitary
		X	aorta	X	kidneys	X	prostate
		X	bone marrow	X	larynx	X	rectum
		X	brain (3	X	liver	X	salivary glands
			regions)	X	lungs	X	seminal
		X	cecum	X	lymph nodes		vesicule
		X	colon	X	musculature	X	skin
		X	duodenum	X	mammary	X	spinal cord (3X)
		X	heart		gland	X	spleen
		X	epididymides	X	nose	X	stomach
		X	esophagus	X	ovaries	X	testes
		X	eyes	X	oviduct	X	thymus
		NA	gall bladder	X	pancreas	X	thyroid
			(if present)	X	parathryoids	X	trachea
		X	heart	X	peripheral	X	urinary bladder
		X	ileum		nerve	X	uterus
				X	pharynx		

*Not indicated as required in 1998 OPPTS Harmonized Test Guidelines: Vagina Zymbol glands. All tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246311

870.3100 Subchronic 90-Day Oral Toxicity in Rodents - Rat - Gavage

Does this study meet the following acceptance criteria?

No.	Yes/ No	Criteria
1	**Y**	Study conducted under GLP (with statement).
2	**Y**	Technical form of the active ingredient used
3	**Y**	Full identification of the test material (physical state, color, batch or lot number, expiration date, percentage active).
4	**Y**	Rat is preferred species, although other rodent species can be used.
5	**Y**	Identification as to test animal strain and source.
6	**Y**	Testing started with young healthy animals, no older than 8-9 weeks old for rats.
7	**Y**	At least 10 animals/sex/dose level, with concurrent control group.
8	**NA**	If interim sacrifices, number of animals/group should be increased accordingly.
9	**Y**	Dosing duration of 90 days or 5 days/week for 13 weeks. **Gavage**
10	**Y**	Doses tested include a NOAEL
11	**Y**	Highest dose level produces indications of toxicity or is a limit dose (1000 mg/kg)
12	**Y**	Analyses for test material stability, homogeneity and concentration in dosing medium.
13	**Y**	Individual daily observations.
14	**Y**	Individual body weights (before administration, weekly thereafter, and at death).
15	**Y**	Individual or cage food consumption.
16	**Y**	Ophthalmoscopic examination (pretest & term) for at least control and high dose.
17	**N**	Assessment of motor activity, grip strength, reactivity to sensory stimuli (not earlier than week 11).

18	**Y**	Hematology a d clinical chemistry at termination.
19		**Hematology** __X__ Erythr cyte count _____ Leukocyte count __X__ Diff rential count __X__ Hemoglobin __X__ Hem tocrit __X__ Mea corpuscular hemoglobin. __X__ Mean corpuscular volume __X__ Mea corpuscular hemoglobin. concentration __X__ Platelet count __X__ Prot rombin time or activated partial thromboplastin time.
20		**Clinical Che istry** __X__ Pota sium __X__ Urea nitrogen __X__ T3 __X__ Sodi m __X__ Creatinine __X__ T4 __X__ Ala ine aminotransferase __X__ TSH __X__ Asp rtate aminotransferase __X__ Alka ine phosphatase __X__ Glu ose __X__ Total protein __X__ Alb min __X__ Total cholesterol __-__ Ch linesterases (if appropriate.)
21*		**Urinalysis** (c otional; during last week: parameters include: __X__ a pearance, __X__ volume, __X__ osmolality or specific gravi y, __X__ pH, __X__ protein, __X__ glucose, and __X__ blood or blood cells.
22	**Y**	Individual gr ss necropsy of all animals
23	**Y**	**Organ weig ts:** __X__ Liv r __X__ Ovaries __X__ Spleen __X__ Kidn ys _____ Uterus __X__ Brain __X__ Adr nals _____ Thymus __X__ Heart __X__ Tes es (with Epididymides)
24	**Y**	Full histopat ology of the following tissues from at least all control and high-doseani nals, and all rodents that died or were killed during the study, all gross lesi ns in all animals, and target tissues in all animals.

25		X adrenals	X jejunum	X pituitary
		X aorta	X kidneys	X prostate
		X bone marrow	X larynx	X rectum
		X brain (3 regions)	X liver	X salivary glands
		X cecum	X lungs	X seminal vesicle
		X colon	X lymph nodes	X skin
		X duodenum	X musculature	X spinal cord (3X)
		X heart	X mammary gland	X spleen
		X epididymides	X nose	X stomach
		X esophagus	X ovaries	X testes
		X eyes	X oviduct	X thymus
		NA gallbladder (if present)	X pancreas	X thyroid
			X parathyroids	X trachea
		X heart	X peripheral nerve	X urinary bladder
		X ileum	X pharynx	X uterus

§Not indicated as required in 1998 OPPTS Harmonized Test Guidelines: Vagina Zymbol glands and all tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: JAU6476- K Salt PC Code: 113961 MRID No.: 46246312

870.3100 Subchronic 90-Day Oral Toxicity in Rodents - Rat - Diet

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	**Y**	Study conducted under GLP (with statement).
2	**Y**	Technical form of the active ingredient used
3	**Y**	Full identification of the test material (physical state, color, batch or lot number, expiration date, percentage active).
4	**Y**	Rat is preferred species, although other rodent species can be used.
5	**Y**	Identification as to test animal strain and source.
6	**Y**	Testing started with young healthy animals, no older than 8-9 weeks old for rats.
7	**Y**	At least 10 animals/sex/dose level, with concurrent control group.
8	**NA**	If interim sacrifices, number of animals/group should be increased accordingly.
9	**Y**	Dosing duration of 90 days or 5 days/week for 13 weeks. **Dietary**
10	**Y**	Doses tested include a NOAEL
11	**Y**	Highest dose level produces indications of toxicity or is a limit dose (1000 mg/kg)
12	**Y**	Analyses for test material stability, homogeneity and concentration in dosing medium.
13	**Y**	Individual daily observations.
14	**Y**	Individual body weights (before administration, weekly thereafter, and at death).
15	**Y**	Individual or cage food consumption.
16	**Y**	Ophthalmoscopic examination (pretest & term) for at least control and high dose.
17	**N**	Assessment of motor activity, grip strength, reactivity to sensory stimuli (not earlier than week 11).

18	**Y**	Hematology and clinical chemistry at termination.
19	**Y**	**Hematology** __X__ Erythrocyte count __X__ Leukocyte count _____ Differential count __X__ Hemoglobin __X__ Hematocrit __X__ Mean corpuscular hemoglobin __X__ Mean corpuscular volume __X__ Mean corpuscular hemoglobin. concentration __-__ Platelet count __-__ Prothrombin time or activated partial thromboplastin time.
20	**Y**	**Clinical Chemistry** __X__ Potassium __X__ Urea nitrogen __X__ T3 __X__ Sodium __X__ Creatinine __X__ T4 __X__ Alanine aminotransferase __X__ TSH __X__ Aspartate aminotransferase __X__ Alkaline phosphatase __X__ Glucose __X__ Total protein __X__ Albumin __X__ Total cholesterol _____ Cholinesterases (if appropriate.)
21[2]	**Y**	**Urinalysis** (optional; during last week): parameters include: __x__ appearance, __x__ volume, __x__ osmolality or specific gravity, __x__ pH, __x__ protein, __x__ glucose, and __x__ blood or blood cells.
22	**Y**	Individual gross necropsy of all animals.
23	**N**	**Organ weights:** _____ Liver _____ Ovaries _____ Spleen _____ Kidneys _____ Uterus _____ Brain _____ Adrenals _____ Thymus _____ Heart _____ Testes (with Epididymides)
24	**Y**	Full histopathology of the following tissues from at least all control and high-doseanimals, and all rodents that died or were killed during the study, all gross lesions in all animals, and target tissues in all animals.

[2]Not indicated as required in 1998 OPPTS Harmonized Test Guidelines.

25	**Y**	X adrena ls	X jejunum	X pituitary
		X aorta	X kidneys	X prostate
		X bone ı ıarrow	X larynx	X rectum
		X brain 3 regions)	X liver	X salivary glands
		X cecun	X lungs	X seminal vesicle
		X colon	X lymph nodes	X skin
		X duode ıum	X musculature	X spinal cord(3X)
		X hear	X mammary gland	X spleen
		X epid dymides	X nose	X stomach
		X esop ıagus	X ovaries	X testes
		X eyes	X oviduct§	X thymus
		NA gall ıladder (if pres ent)	X pancreas	X thyroid
			X parathyroids	X trachea
		X hear	X peripheral nerve	X urinary bladder
		X ileu ı	X pharynx	X uterus
		Vagina Zymb ıl glands and all tissues with abnormalities.		

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246310

870.3100 Subchronic 90-Day Oral Toxicity in Rodents - Mice - Diet

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	**Y**	Study conducted under GLP (with statement).
2	**Y**	Technical form of the active ingredient used
3	**Y**	Full identification of the test material (physical state, color, batch or lot number, expiration date, percentage active).
4	**Mouse**	Rat is preferred species, although other rodent species can be used.
5	**Y**	Identification as to test animal strain and source.
6	**Y**	Testing started with young healthy animals, no older than 8-9 weeks old for rats.
7	**Y**	At least 10 animals/sex/dose level, with concurrent control group.
8	**NA**	If interim sacrifices, number of animals/group should be increased accordingly.
9	**Y**	Dosing duration of 90 days or 5 days/week for 13 weeks - **Dietary**.
10	**No**	Doses tested include a NOAEL **A NOAEL was not established**.
11	**Y**	Highest dose level produces indications of toxicity or is a limit dose (1000 mg/kg)
12	**Y**	Analyses for test material stability, homogeneity and concentration in dosing medium.
13	**Y**	Individual daily observations.
14	**Y**	Individual body weights (before administration, weekly thereafter, and at death).
15	**Y**	Individual or cage food consumption.
16	**X**	Ophthalmoscopic examination (pretest & term) for at least control and high dose. Only at end of treatment.
17	**N**	Assessment of motor activity, grip strength, reactivity to sensory stimuli (not earlier than week 11).
18	**Y**	Hematology and clinical chemistry at termination.

19	Y	**Hematology** __x__ Erythrocy e count __x__ Leukocyte count __x__ Different al count __x__ Hemoglobin __x__ Hematoc rit __x__ Mean cor puscular hemoglobin. __x__ Mean corpuscular volume __x__ Mean co puscular hemoglobin. concentration __x__ Platelet c unt __No__ Prothrc nbin time or activated partial thromboplastin time.
20	Y	**Clinical Chemis ry** __N__ Potassi m __x__ Urea nitrogen __N__ Sodium __x__ Creatinine __x__ Alanine aminotransferase __x__ Aspartat e aminotransferase __x__ Alkaline phosphatase __N__ Glucose __x__ Total protein __x__ Albumi __x__ Total cholesterol _____ Cholines erases (if appropriate.)
21*	N	**Urinalysis** (opti nal; during last week: parameters include: appearance, volume, osmolality or spe cific gravity, pH, protein, glucose, and blood or blood cells. **Not required or recorded for mice.**
22	Y	Individual gross necropsy of all animals
23	Y	**Organ weights** __x__ Liver __x__ Ovaries __x__ Spleen __x__ Kidney __N__ Uterus __x__ Brain __x__ Adrena s __N__ Thymus __x__ Heart __x__ Testes (with Epididymides) __x__ Lungs
24	Y	Full histopathol gy of the following tissues from at least all control and high-doseanimals, an all rodents that died or were killed during the study, all gross lesions in all ani nals, and target tissues in all animals.

25	Y	_x_ adrenals	_x_ jejunum	_x_ pituitary
		_x_ aorta	_x_ kidneys	_x_ prostate
		_x_ bone marrow	_x_ larynx	_x_ rectum
		_x_ brain (3 regions)	_x_ liver	_x_ salivary glands
		_x_ cecum	_x_ lungs	_x_ seminal vesicle
		_x_ colon	_x_ lymph nodes	_x_ skin
		_x_ duodenum	_x_ musculature	_x_ spinal cord (3X)
		_x_ heart	_x_ mammary gland	_x_ spleen
		_x_ epididymides	_x_ nose	_x_ stomach
		_x_ esophagus	_x_ ovaries	_x_ testes
		_x_ eyes	_x_ oviduct§	_x_ thymus
		_x_ gallbladder (if present)	_x_ pancreas	_x_ thyroid
			_x_ parathyroids	_x_ trachea
		_x_ heart	_x_ peripheral nerve	_x_ urinary bladder
		_x_ ileum	_x_ pharynx	_x_ uterus

*Not indicated as required in 1998 OPPTS Harmonized Test Guidelines: Vagina Zymbol glands of all tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246313

870.3150 Subchronic 90-Day Oral Toxicity in Non Rodents - Dog - Gavage

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study conducted under GLP (with statement).
2	Y	Technical form of the active ingredient used.
3	Y	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date)
4	Y	Dog used (preferred species); otherwise justification for species used.
5	Y	Identification as to test animal breed (usually beagle) and source..
6	Y	Preferably 4-6 months, but no older than 9 months of age at start of dosing.
7	Y	At least 8 (4M & 4F) animals/dose level , with concurrent control group.
8	NA	If interim sacrifices, number of animals/group increased accordingly.
9	Y	Dosing duration of 90 days or 5 days/week for 13 weeks.
10	Y	Adequate randomization for proper allocation of animals to test & control groups.
11	Y	Doses tested include a NOAEL
12	Y	Highest dose level produces indications of toxicity or is a limit dose (1000 mg/kg).
13	Y	Analyses for test material stability, homogeneity and concentration in dosing medium
14	Y	Individual daily observations (includes 2X/day for morbidity and mortality)
15	Y	Individual clinical exams prior to initiation and at least once weekly thereafter.
16	Y	Individual body weights (before administration, weekly thereafter, and at termination.
17	Y	Individual food and water consumption.
18	Y	Ophthalmoscopic examination (pretest & term) for at least control and high dose.
19	Y	Hematology and clinical chemistry at termination.

20	Y	**Hematology** __X__ Erythrocyte count __X__ Leukocyte count _____ Differential count __X__ Hematocrit __X__ Hemoglobin concentration. __X__ Mean corpuscular hemoglobin. __X__ Mean corpuscular volume __X__ Mean corpuscular. hemoglobin concentration __X__ Platelet count __X__ Prothrombin time or activated partial thromboplastin time
21	Y	**Clinical Chemistry** (indicates "suggested" measurements): __X__ Calcium __X__ Potassium __X__ Sodium __X__ Phosphorus __X__ Chloride __X__ Total cholesterol __X__ Urea nitrogen __X__ Creatinine __X__ Total protein __X__ Total bilirubin __X__ Glucose __X__ Albumin __X__ Alanine aminotransferase __X__ Aspartate aminotransferase __X__ Alkaline phosphatase __X__ Sorbitol dehydrogenase __X__ Gamma glutamyl transpep. _____ Cholinesterases (if appropriate) _____ Others (fasting triglycerides, hormones, methemoglobin), if appropriate
22	Y	**Urinalysis** (prior to treatment, midway through, and at the end of the study, using timed urine collection). __Y__ Appearance __Y__ pH __Y__ Glucose __Y__ Volume __Y__ Protein __Y__ Blood or blood cells __Y__ Osmolality or specific gravity
23	Y	**Organ weights** (weighed wet as soon as possible after dissection). __X__ Liver & Gall Bladder _____ Epididymides __X__ Thymus __X__ Kidneys __X__ Ovaries __X__ Lungs __X__ Spleen __X__ Adrenals _____ Uterus __X__ Thyroid __X__ Brain __X__ Testes __X__ Heart __X__ Pituitary __X__ Thyroid & Parathyroids .

24	Y	Full histopatho ogy of the following tissues from at least all control and high-dose animals (v ith extension to all animals in all dosage groups if treatment-related change: are observed in the high-dose group) and all animals that died or were killed dur ng the study, all gross lesions in all animals, and target tissues in all animals.
25	Y	X adren ils X jejunum X pituitary X aorta X kidneys X prostate X bone narrow X larynx X rectum X brain (3 regions) X liver X salivary glands X cecu n X lungs _____ seminal vesicle X color X lymph nodes X skin _____ duod num X musculature X spinal cord (3X) X heart X mammary gland X spleen X epidi lymides X nose X stomach X esopl agus X ovaries X testes X eyes X oviduct X thymus X gallb adder X pancreas X thyroid (if pr sent) X parathyroids X trachea _____ heart X peripheral nerve X urinary X ileum _____ pharynx X uterus

Vagina Zymbol glands of all tissue: with abnormalities.

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246314

870.3150 Subchronic 90-Day Oral Toxicity in Non Rodents - Dog - Diet

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study conducted under GLP (with statement).
2	Y	Technical form of the active ingredient used.
3	Y	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date)
4	Y	Dog used (preferred species); otherwise justification for species used.
5	Y	Identification as to test animal breed (usually beagle) and source..
6	Y	Preferably 4-6 months, but no older than 9 months of age at start of dosing.
7	Y	At least 8 (4M & 4F) animals/dose level , with concurrent control group.
8	NA	If interim sacrifices, number of animals/group increased accordingly.
9		Dosing duration of 90 days or 5 days/week for 13 weeks. **Dietary**
10	Y	Adequate randomization for proper allocation of animals to test & control groups.
11	Y	Doses tested include a NOAEL
12	Y	Highest dose level produces indications of toxicity or is a limit dose (1000 mg/kg).
13	Y	Analyses for test material stability, homogeneity and concentration in dosing medium
14	Y	Individual daily observations (includes 2X/day for morbidity and mortality)
15	Y	Individual clinical exams prior to initiation and at least once weekly thereafter.
16	Y	Individual body weights (before administration, weekly thereafter, and at termination.
17	Y	Individual food and water consumption.
18	Y	Ophthalmoscopic examination (pretest & term) for at least control and high dose.

19	Y	Hematology and clinical chemistry at termination.
20	Y	**Hematology** __X__ Erythrocyte count __X__ Leukocyte count _____ Differential count __X__ Hematocrit __X__ Hemoglobin concentration. __X__ Mean corpuscular hemoglobin. __X__ Mean corpuscular volume __X__ Mean corpuscular. hemoglobin concentration __X__ Platelet count __X__ Prothrombin time or activated partial thromboplastin time
21	Y	**Clinical Chemistry** (indicates "suggested" measurements): __X__ Calcium __X__ Potassium __X__ Sodium __X__ Phosphorus __X__ Chloride __X__ Total cholesterol __X__ Urea nitrogen __X__ Creatinine __X__ Total protein __X__ Total bilirubin __X__ Glucose __X__ Albumin __X__ Alanine aminotransferase __X__ Aspartate aminotransferase __X__ Alkaline phosphatase _____ Sorbitol dehydrogenase __X__ Gamma glutamyl transpep. __X__ Cholinesterases (if appropriate) _____ Others (fasting triglycerides, hormones, methemoglobin), if appropriate
22	Y	**Urinalysis** (prior to treatment, midway through, and at the end of the study, using timed urine collection). __X__ Appearance __X__ pH __X__ Glucose __X__ Volume __X__ Protein __X__ Blood or blood cells _____ Osmolality or specific gravity
23	Y	**Organ weights** (weighed wet as soon as possible after dissection). __X__ Liver & Gall Bladder _____ Epididymides _____ Thymus __X__ Kidneys __X__ Ovaries __X__ Lungs __X__ Spleen __X__ Adrenals _____ Uterus __X__ Pancreas __X__ Brain __X__ Testes __X__ Prostate __X__ Thyroid & Parathyroids __X__ Heart

24	Y	Full histopathology of the following tissues from at least all control and high-dose animals (with extension to all animals in all dosage groups if treatment-related changes are observed in the high-dose group) and all animals that died or were killed during the study, all gross lesions in all animals, and target tissues in all animals.
25	Y	X adrenals X jejunum X pituitary X aorta X kidneys X prostate X bone marrow X larynx ____ rectum X brain (3 regions) X liver X salivary glands X cecum X lungs ____ seminal vesicle X colon X lymph nodes X skin X duodenum X musculature§ X spinal cord (3X) X heart X mammary gland X spleen X epididymides X nose X stomach X esophagus X ovaries X testes X eyes X oviduct§ X thymus X gallbladder (if present) X pancreas X thyroid X parathyroids X trachea X heart X peripheral nerve X urinary bladder X ileum X pharynx X uterus

Vagina Zymbol glands of all tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246315

870 3200 21/28 Day Dermal Toxicity

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study conducte . under GLP (with statement).
2	?	Technical form of the active ingredient used.
3		Full identificati n of the test material (chemical identification, percentage active,batch or ot number, physical properties, purity/impurities, expiration date, vehicle used, if any) ***Undiluted solid. "Content = 98.5%."***
4	**Y**	Rat, rabbit, or g uinea pig used. If another species, then justification provided
5	**Y**	Identification a to test animal strain and source.
6	**Y**	Age at start of osing: rat: 8-9 wks; rabbit: at least 12 wks; guinea pig: 5-6 weeks. ***♂9 wks ♀ 10 wks***
7	**Y**	For risk assessi ient, 10 animals/sex/dose level, with concurrent vehicle control group.
8	**N/A**	For screening s udies, 5/sex/dose level, with concurrent control group
9	**N/A**	If interim sacri ices, number of animals/group increased accordingly.
10	**N**	Liquid test sub tances applied undiluted except when severe skin irritation results; solids p ulverized when possible, and moistened with water or a suitable vehicle for goc l skin contact.
11		Treatment for t least 6 h/day ***(Yes)***, 5 days/wk ***(Yes)***, dosing at about same time each day ***(?)***.
12	**Y**	Fur clipped fi om at least 10% of body surface area, test substance applied uniformly ov r the treatment site, and during exposure test substance held in contact with sk in with a porous gauze dressing (≤8 ply).
13	**Y**	Doses tested in clude a NOAEL. ***HDT 1000 mg/kg*** **(see page 26)**
14	**Y**	Highest dose l vel produces indications of toxicity or is a limit dose (1000 mg/kg)
15	**Y**	Individual dail y observations (includes 2X/day for morbidity and mortality). **?** ***No animal die d.***

16	**Y**	Individual clinical exams prior to initiation and at least once weekly afterwards
17	**Y**	Individuall body weights (before administration, weekly thereafter, and at term).
18	**Y**	Food consumption should be measured on a weekly basis.
19	**N/A**	Assessment of motor activity, grip strength, reactivity to sensory stimuli (near the end of exposure period) ***NO***
20	**Y**	Ophthalmoscopic examination on all pre-exposure and on at least control and high dose just before termination.
21	**Y**	Individual necropsy of all animals
22	**Y**	Hematology and clinical chemistry at termination
23	**Y**	**Hematology** __X__ Erythrocyte count_ __X__ Leukocyte count __X__ Differential count __X__ Hematocrit __X__ Hemoglobin concentration. __X__ Mean corpuscular volume __X__ Mean corpuscualr hemoglobin. __X__ Mean corpuscualr hemoglobin concentario __X__ Platelet count __X__ Prothrombin time or activated partial thromboplastin time
24	**Y**	**Clinical Chemistry** __X__ Calcium[1] __X__ Phosphorus[1] __X__ Potassium __X__ Total cholesterol __X__ Sodium __X__ Urea nitrogen _____ Creatinine __X__ Total protein __X__ Glucose __X__ Albumin __X__ Alanine aminotransferase[2] __X__ Aspartate aminotransferase[2] __X__ Alkaline phosphatase[2] __X__ Sorbitol dehydrogenase[2] __X__ Gamma glutamyl transpep[2] __X__ Cholinesterases[1] __X__ Hormones[1] __X__ Methemoglobin[1] __X__ Fasting triglycerides[1]
25	**Optional** **No**	**Urinalysis** (optional, performed during the last week of the study using timed. urine volume collection). No. __X__ Appearance _____ pH __X__ Glucose __X__ Volume _____ Protein __X__ Blood or blood cells __X__ Osmolality or specific gravity

26	**Y**	Organ weights (veighed wet as soon as possible after dissection). __X__ Liver __X__ Epididymides __X__ Thymus __X__ Kidne s __X__ Ovaries __X__ Spleen __X__ Adren ls __X__ Uterus __X__ Brain __X__ Testes __X__ Heart
27	All tissues OK, except bone marrow.	_____ Preserv tion of the following tissues, with full histopathology from all control and higl -dose animals (extension to all dosage groups if treatment-related changes are obs erved in the high-dose group) and from all animals that died or were killed dur ıg the study, along with gross lesions and target tissues in all animals. __X__ adren ls __X__ jejunum __X__ pituitary __X__ aorta __X__ kidneys __X__ prostate _____ bone narrow __X__ larynx __X__ rectum __X__ brai (3 regions) __X__ liver __X__ salivary glands __X__ cecum __X__ lungs __X__ seminal vesicle __X__ colon __X__ lymph nodes __X__ skin __X__ duode ıum _____ musculature __X__ spinal cord (3X) _____ heart __X__ mammary gland __X__ spleen __X__ epidic ymides __X__ nose __X__ stomach _____ esoph ıgus __X__ ovaries __X__ testes __X__ eyes _____ oviduct __X__ thymus _____ gallbl ıdder (if prese t) __X__ pancreas __X__ thyroid __X__ heart __X__ parathyroids __X__ trachea _____ peripheral nerve __X__ urinary bladder _____ ileum __X__ pharynx __X__ uterus

[1]Measurement that should be made f test material is known or suspected of affecting this or a related parameter.

[2]Activity of more than two of these ıepatic enzymes should be measured. Not indicated as a required tissue in 1998 OPPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246316

870.3700a Prenatal Develpomental Toxicity Study - Rat Oral

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2	Y	Technical form of the active ingredient used
3	Y	Full identification of the test material (chemical identification, percentage active batch or lot number, physical properties purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4*	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
5	Y	Preferred species are rat (rodent) and rabbit (nonrodent).
6	Y	Identification as to test animal strain and source.
7	Y	Young adult animals should be used; females should be nulliparous, and the should be mated with males of the same species and strain, avoiding the mating of siblings, if parentage is known.
8	Y	Normally (except when a limit dose of 1000 mg/kg/day shows no effects) there should three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects.
9	Y	At the highest dose level, there should be significant maternal toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day by the oral or dermal exposure routes)
10	Y	The lowest dose level should not produce any evidence of either maternal or developmental toxicity.
11	Y	The test substance should be administered daily from implantation to the day before cesarean section (one day prior to the expected day of parturition). If preliminary studies indicate a low potential for preimplantation loss, treatment may be from fertilization to 1 day prior to the expected day of termination
12	Y	Each test and control group should contain a sufficient number of animals to yield approximately 20 animals with implantation sites at necropsy. [Note: if rabbit is used and the study was initiated or completed before January 2000 then 12 animals/dose level may be acceptable)
13	Y	Individual daily observations.

14	Y	Individual b dy weights (on day 0, at termination, and at least at 3-day intervals du ing the dosing periods.
15	Y	Individual f od consumption (on at least 3-day intervals, preferably on days when body v eights are recorded).
16	Y	Reporting o gravid uterine weights, as well as body weight changes adjusted for gravid u erine weights
17	Y	Individual u erine examination for implantation data, number of viable (by sex) and dea d fetuses, and early and late resorptions. Uteri that appear to be non-gravid s hould be examined by a technique (such as ammonium sulfide staining) to onfirm nonpregnant status.
18	Y	All ovarie examined to determine number of corpora lutea.
19	Y	Sex and boc y weight of each fetus determined. Report should include fetal body weigh t data, preferably by sex and with sexes combined
20	Y	Each fetus e xamined for external anomalies.
21	Y	For rodents approximately one-half of each litter prepared by standard techniques a nd examined for skeletal alterations. Remainder appropriately prepared an l examined for soft tissue anomalies. Also acceptable: examination of all fetuse s by careful dissection for soft tissue anomalies followed by examinatio for skeletal anomalies.
22	–	For rabbits, all fetuses examined for both soft tissue and skeletal alterations. An adequat evaluation of the internal structures of the head, including the eye, brain, nasal passages, and tongue, should be conducted on at least half the fetuses.
23	Y	Historical ontrol data with litter incidence and fetal incidence within litter[usuall / from the performing laboratory], including dates of studies, strain and source of animals, and the vehicle(s) and route(s) of administration, when appropriate to enhance the interpretation of study results.

*Preferred, but not specified in the)PPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: SXX 0665 PC Code: 113961 MRID No.: 46246321

870.3700a Prenatal Develpomental Toxicity Study - Rat Oral

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2	Metabolite	Technical form of the active ingredient used
3	Y	Full identification of the test material (chemical identification, percentage active batch or lot number, physical properties purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4[3]	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
5	Y	Preferred species are rat (rodent) and rabbit (nonrodent).
6	Y	Identification as to test animal strain and source.
7	Y	Young adult animals should be used; females should be nulliparous, and the should be mated with males of the same species and strain, avoiding the mating of siblings, if parentage is known.
8	Y	Normally (except when a limit dose of 1000 mg/kg/day shows no effects) there should three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects.
9	Y	At the highest dose level, there should be significant maternal toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day by the oral or dermal exposure routes)
10	Y	The lowest dose level should not produce any evidence of either maternal or developmental toxicity.
11	Y	The test substance should be administered daily from implantation to the day before cesarean section (one day prior to the expected day of parturition). If preliminary studies indicate a low potential for preimplantation loss, treatment may be from fertilization to 1 day prior to the expected day of termination

12	Y	Each test a d control group should contain a sufficient number of animals to yield appro imately 20 animals with implantation sites at necropsy. [Note: if rabbit is us d and the study was initiated or completed before January 2000 then 12 an mals/dose level may be acceptable)
13	Y	Individual aily observations.
14	Y	Individual ody weights (on day 0, at termination, and at least at 3-day *intervals d uring the dosing periods.*
15	Y	Individual food consumption (on at least 3-day intervals, preferably on days when body weights are recorded).
16	Y	Reporting f gravid uterine weights, as well as body weight changes adjusted for gravid terine weights
17	Y	Individual uterine examination for implantation data, number of viable (by sex) and d ad fetuses, and early and late resorptions. Uteri that appear to be non-gravid should be examined by a technique (such as ammonium sulfide staining) t confirm nonpregnant status.
18	Y	All ovari s examined to determine number of corpora lutea.
19	Y	Sex and b dy weight of each fetus determined. Report should include fetal body weig ht data, preferably by sex and with sexes combined
20	Y	Each fetus examined for external anomalies.
21	Y	For rodent , approximately one-half of each litter prepared by standard techniques and examined for skeletal alterations. Remainder appropriately prepared a id examined for soft tissue anomalies. Also acceptable: examinati n of all fetuses by careful dissection for soft tissue anomalies followed b y examination for skeletal anomalies.
22	—	For rabbit , all fetuses examined for both soft tissue and skeletal alterations. An adequ te evaluation of the internal structures of the head, including the eye, brain, nasal passages, and tongue, should be conducted on at least half the fetuses.
23	Y	Historica control data with litter incidence and fetal incidence within litter [usually fr om the performing laboratory], including dates of studies, strain and sourc of animals, and the vehicle(s) and route(s) of administration, when appropria e to enhance the interpretation of study results.

*Preferred, but not specified in the OPPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246323

870.3700a Prenatal Develpomental Toxicity Study - Rat Dermal

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2	Y	Technical form of the active ingredient used
3	Y	Full identification of the test material (chemical identification, percentage active batch or lot number, physical properties purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4[4]	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
5	Y	Preferred species are rat (rodent) and rabbit (nonrodent).
6	Y	Identification as to test animal strain and source.
7	Y	Young adult animals should be used; females should be nulliparous, and the should be mated with males of the same species and strain, avoiding the mating of siblings, if parentage is known.
8	***One Dose***	Normally (except when a limit dose of 1000 mg/kg/day shows no effects) there should three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects.
9	***One Dose***	At the highest dose level, there should be significant maternal toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day by the oral or dermal exposure routes)
10	Y	The lowest dose level should not produce any evidence of either maternal or developmental toxicity.
11	Y	The test substance should be administered daily from implantation to the day before cesarean section (one day prior to the expected day of parturition). If preliminary studies indicate a low potential for preimplantation loss, treatment may be from fertilization to 1 day prior to the expected day of termination
12	Y	Each test and control group should contain a sufficient number of animals to yield approximately 20 animals with implantation sites at necropsy. [Note: if rabbit is used and the study was initiated or completed before January 2000 then 12 animals/dose level may be acceptable)

13	Y	Individual d ily observations.
14	Y	Individual b dy weights (on day 0, at termination, and at least at 3-day intervals du ing the dosing periods.
15	Y	Individual f od consumption (on at least 3-day intervals, preferably on days when body v eights are recorded).
16	Y	Reporting o gravid uterine weights, as well as body weight changes adjusted for gravid u erine weights
17	Y	Individual u erine examination for implantation data, number of viable (by sex) and de d fetuses, and early and late resorptions. Uteri that appear to be non-gravid : hould be examined by a technique (such as ammonium sulfide staining) to :onfirm nonpregnant status.
18	Y	All ovarie s examined to determine number of corpora lutea.
19	Y	Sex and bo y weight of each fetus determined. Report should include fetal body weig t data, preferably by sex and with sexes combined
20	Y	Each fetus e xamined for external anomalies.
21	Y	For rodents approximately one-half of each litter prepared by standard techniques nd examined for skeletal alterations. Remainder appropriately prepared an l examined for soft tissue anomalies. Also acceptable: examination of all fetuse s by careful dissection for soft tissue anomalies followed by examinatio for skeletal anomalies.
22	N	For rabbits, all fetuses examined for both soft tissue and skeletal alterations. An adequat evaluation of the internal structures of the head, including the eye, brain, nasal passages, and tongue, should be conducted on at least half the fetuses.
23	Y	Historical ontrol data with litter incidence and fetal incidence within litter[usual y from the performing laboratory], including dates of studies, strain and source of animals, and the vehicle(s) and route(s) of administration, when appropriate to enhance the interpretation of study results.

*Preferred, but not specified in the OPPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: JAU6476 Acid K Salt PC Code: 113961 MRID No.: 46246324

870.3700a Prenatal Develpomental Toxicity Study - Rat Oral

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2	Y (Salt)	Technical form of the active ingredient used
3	Y	Full identification of the test material (chemical identification, percentage active batch or lot number, physical properties purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4*	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
5	Y	Preferred species are rat (rodent) and rabbit (nonrodent).
6	Y	Identification as to test animal strain and source.
7	Y	Young adult animals should be used; females should be nulliparous, and the should be mated with males of the same species and strain, avoiding the mating of siblings, if parentage is known.
8	Y	Normally (except when a limit dose of 1000 mg/kg/day shows no effects) there should three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects.
9	Y	At the highest dose level, there should be significant maternal toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day by the oral or dermal exposure routes)
10	Y	The lowest dose level should not produce any evidence of either maternal or developmental toxicity.
11	Y	The test substance should be administered daily from implantation to the day before cesarean section (one day prior to the expected day of parturition). If preliminary studies indicate a low potential for preimplantation loss, treatment may be from fertilization to 1 day prior to the expected day of termination
12	Y	Each test and control group should contain a sufficient number of animals to yield approximately 20 animals with implantation sites at necropsy. [Note: if rabbit is used and the study was initiated or completed before January 2000 then 12 animals/dose level may be acceptable)
13	Y	Individual daily observations.

14	Y	Individual b dy weights (on day 0, at termination, and at least at 3-day intervals du ing the dosing periods.
15	Y	Individual f od consumption (on at least 3-day intervals, preferably on days when body v eights are recorded).
16	Y	Reporting o gravid uterine weights, as well as body weight changes adjusted for gravid u erine weights
17	Y	Individual u erine examination for implantation data, number of viable (by sex) and dea d fetuses, and early and late resorptions. Uteri that appear to be non-gravid s hould be examined by a technique (such as ammonium sulfide staining) to onfirm nonpregnant status.
18	Y	All ovarie examined to determine number of corpora lutea.
19	Y	Sex and boc y weight of each fetus determined. Report should include fetal body weigh t data, preferably by sex and with sexes combined
20	Y	Each fetus e xamined for external anomalies.
21	Y	For rodents approximately one-half of each litter prepared by standard techniques a nd examined for skeletal alterations. Remainder appropriately prepared an l examined for soft tissue anomalies. Also acceptable: examination of all fetuse s by careful dissection for soft tissue anomalies followed by examinatio for skeletal anomalies.
22	X	For rabbits, all fetuses examined for both soft tissue and skeletal alterations. An adequat evaluation of the internal structures of the head, including the eye, brain, nasal passages, and tongue, should be conducted on at least half the fetuses.
23	Y	Historical control data with litter incidence and fetal incidence within litter[usuall y from the performing laboratory], including dates of studies, strain and source of animals, and the vehicle(s) and route(s) of administration, when appropriate to enhance the interpretation of study results.

*Preferred, but not specified in the OPPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246325

870.3700a Prenatal Develpomental Toxicity Study - Rat Dermal

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2	Metabolite	Technical form of the active ingredient used
3	Y	Full identification of the test material (chemical identification, percentage active batch or lot number, physical properties purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4*	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
5	Y	Preferred species are rat (rodent) and rabbit (nonrodent).
6	Y	Identification as to test animal strain and source.
7	Y	Young adult animals should be used; females should be nulliparous, and the should be mated with males of the same species and strain, avoiding the mating of siblings, if parentage is known.
8	Y	Normally (except when a limit dose of 1000 mg/kg/day shows no effects) there should three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects.
9	Y	At the highest dose level, there should be significant maternal toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day by the oral or dermal exposure routes)
10	N	The lowest dose level should not produce any evidence of either maternal or developmental toxicity.
11	Y	The test substance should be administered daily from implantation to the day before cesarean section (one day prior to the expected day of parturition). If preliminary studies indicate a low potential for preimplantation loss, treatment may be from fertilization to 1 day prior to the expected day of termination
12	Y	Each test and control group should contain a sufficient number of animals to yield approximately 20 animals with implantation sites at necropsy. [Note: if rabbit is used and the study was initiated or completed before January 2000 then 12 animals/dose level may be acceptable)
13	Y	Individual daily observations.

14	Y	Individual l ody weights (on day 0, at termination, and at least at 3-day intervals d: ring the dosing periods.
15	Y	Individual ood consumption (on at least 3-day intervals, preferably on days when body weights are recorded).
16	Y	Reporting (f gravid uterine weights, as well as body weight changes adjusted for gravid u terine weights
17	Y	Individual terine examination for implantation data, number of viable (by sex) and de ıd fetuses, and early and late resorptions. Uteri that appear to be non-gravid should be examined by a technique (such as ammonium sulfide staining) tc confirm nonpregnant status.
18	Y	All ovari s examined to determine number of corpora lutea.
19	Y	Sex and bc ly weight of each fetus determined. Report should include fetal body weig ıt data, preferably by sex and with sexes combined
20	Y	Each fetus examined for external anomalies.
21	Y	For rodent , approximately one-half of each litter prepared by standard techniques and examined for skeletal alterations. Remainder appropriately prepared a ıd examined for soft tissue anomalies. Also acceptable: examinatic n of all fetuses by careful dissection for soft tissue anomalies followed b / examination for skeletal anomalies.
22	X	For rabbits , all fetuses examined for both soft tissue and skeletal alterations. An adequa e evaluation of the internal structures of the head, including the eye, brain, nasal passages, and tongue, should be conducted on at least half the fetuses
23	Y	Historical control data with litter incidence and fetal incidence within litter[usua ly from the performing laboratory], including dates of studies, strain and source of animals, and the vehicle(s) and route(s) of administration, when appı opriate to enhance the interpretation of study results.

*Preferred, but not specified in the (PPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246327

870.3700b Prenatal Develpomental Toxicity Study - Rabbit Oral

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2	Metabolite	Technical form of the active ingredient used
3	Y	Full identification of the test material (chemical identification, percentage active batch or lot number, physical properties purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4*	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
5	Y	Preferred species are rat (rodent) and rabbit (nonrodent).
6	Y	Identification as to test animal strain and source.
7	Y	Young adult animals should be used; females should be nulliparous, and the should be mated with males of the same species and strain, avoiding the mating of siblings, if parentage is known.
8	Y	Normally (except when a limit dose of 1000 mg/kg/day shows no effects) there should three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects.
9	Y	At the highest dose level, there should be significant maternal toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day by the oral or dermal exposure routes)
10	Y	The lowest dose level should not produce any evidence of either maternal or developmental toxicity.
11	Y	The test substance should be administered daily from implantation to the day before cesarean section (one day prior to the expected day of parturition). If preliminary studies indicate a low potential for preimplantation loss, treatment may be from fertilization to 1 day prior to the expected day of termination
12	Y	Each test and control group should contain a sufficient number of animals to yield approximately 20 animals with implantation sites at necropsy. [Note: if rabbit is used and the study was initiated or completed before January 2000 then 12 animals/dose level may be acceptable)
13	Y	Individual daily observations.

14	Y	Individual body weights (on day 0, at termination, and at least at 3-day intervals during the dosing periods.
15	Y	Individua food consumption (on at least 3-day intervals, preferably on days when bod weights are recorded).
16	Y	Reporting of gravid uterine weights, as well as body weight changes adjusted for gravid uterine weights
17	Y	Individual uterine examination for implantation data, number of viable (by sex) and d ead fetuses, and early and late resorptions. Uteri that appear to be non-gravi l should be examined by a technique (such as ammonium sulfide staining) t o confirm nonpregnant status.
18	Y	All ova es examined to determine number of corpora lutea.
19	Y	Sex and b ody weight of each fetus determined. Report should include fetal body wei ght data, preferably by sex and with sexes combined
20	Y	Each fetu examined for external anomalies.
21	X	For roden s, approximately one-half of each litter prepared by standard technique ; and examined for skeletal alterations. Remainder appropriately prepared nd examined for soft tissue anomalies. Also acceptable: examinat on of all fetuses by careful dissection for soft tissue anomalies followed by examination for skeletal anomalies.
22	Y	For rabbi s, all fetuses examined for both soft tissue and skeletal alterations. An adequ ate evaluation of the internal structures of the head, including the eye, brair , nasal passages, and tongue, should be conducted on at least half the fetuse s.
23	Y	Historica l control data with litter incidence and fetal incidence within litter[usu lly from the performing laboratory], including dates of studies, strain an source of animals, and the vehicle(s) and route(s) of administ ation, when appropriate to enhance the interpretation of study results.

*Preferred, but not specified in the O PPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246328

870.3700b Prenatal Develpomental Toxicity Study - Rabbit Oral

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2		Technical form of the active ingredient used
3	Y	Full identification of the test material (chemical identification, percentage active batch or lot number, physical properties purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4*	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
5	Y	Preferred species are rat (rodent) and rabbit (nonrodent).
6	Y	Identification as to test animal strain and source.
7	Y	Young adult animals should be used; females should be nulliparous, and the should be mated with males of the same species and strain, avoiding the mating of siblings, if parentage is known.
8	Y	Normally (except when a limit dose of 1000 mg/kg/day shows no effects) there should three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects.
9	Y	At the highest dose level, there should be significant maternal toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day by the oral or dermal exposure routes)
10	Y	The lowest dose level should not produce any evidence of either maternal or developmental toxicity.
11	Y	The test substance should be administered daily from implantation to the day before cesarean section (one day prior to the expected day of parturition). If preliminary studies indicate a low potential for preimplantation loss, treatment may be from fertilization to 1 day prior to the expected day of termination
12	Y	Each test and control group should contain a sufficient number of animals to yield approximately 20 animals with implantation sites at necropsy. [Note: if rabbit is used and the study was initiated or completed before January 2000 then 12 animals/dose level may be acceptable)
13	Y	Individual daily observations.

14	Y	Individual b ›dy weights (on day 0, at termination, and at least at 3-day intervals du ·ing the dosing periods.
15	Y	Individual f ›od consumption (on at least 3-day intervals, preferably on days when body ' /eights are recorded).
16	Y	Reporting o 'gravid uterine weights, as well as body weight changes adjusted for gravid u erine weights
17	Y	Individual u erine examination for implantation data, number of viable (by sex) and de: d fetuses, and early and late resorptions. Uteri that appear to be non-gravid : hould be examined by a technique (such as ammonium sulfide staining) to :onfirm nonpregnant status.
18	Y	All ovarie ; examined to determine number of corpora lutea.
19	Y	Sex and boc y weight of each fetus determined. Report should include fetal body weigl t data, preferably by sex and with sexes combined
20	Y	Each fetus (xamined for external anomalies.
21	-	For rodents approximately one-half of each litter prepared by standard techniques . nd examined for skeletal alterations. Remainder appropriately prepared an l examined for soft tissue anomalies. Also acceptable: examination of all fetuse ; by careful dissection for soft tissue anomalies followed by examinatio . for skeletal anomalies.
22	Y	For rabbits, all fetuses examined for both soft tissue and skeletal alterations. An adequat : evaluation of the internal structures of the head, including the eye, brain, nasal passages, and tongue, should be conducted on at least half the fetuses.
23	Y	Historical :ontrol data with litter incidence and fetal incidence within litter[usual y from the performing laboratory], including dates of studies, strain and source of animals, and the vehicle(s) and route(s) of administration, when appropriate to enhance the interpretation of study results.

*Preferred, but not specified in the (PPTS Harmonized Test Guidelines.

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246333

870.3800 Reproduction and Fertility Effects

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	**Y**	Study conducted under GLP (with statement
2	**Y**	Technical form of the active ingredient used.
3	**Y**	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study.
4	**Y**	Analyses for test material stability, homogeneity and concentration in dosing medium
5	**Y**	Preferred species is rat; if another species is used, justification is needed.
6	**Y**	Identification as to test animal strain and source; strains with low fecundity should not be used.
7	**Y**	Parental (P) animals should be 5 to 9 weeks old at the start of dosing.
8	**Y**	Normally (except when a limit dose of 1000 mg/kg/day or 20,000 ppm in the diet shows no effects) there should be three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects
9	**Y**	At the highest dose level, there should be some reproductive and/or systemic toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day, or 20,000 ppm in the diet)
10	**Y**	The lowest dose level should not produce any evidence of either systemic or reproductive toxicity
11	**Y**	Test substance is usually administered by the oral route (diet, drinking water, or gavage). If another route is used, justification must be provided.
12	**Y**	Dosage must be on a 7-days-a-week basis.
13	**Y**	At least two generations are bred.
14	**Y**	Individual daily observations, with thorough weekly physical examinations
15	Y	Daily dosing of the P and F1 males and females should continue until termination

16	Y	P and F1 ar imals should be individually weighed on the first day of dosing and weekly thereafter. Parental females (P and F1) should be weighed on approximat ely gestation days 0, 7, 14 and 21, and during lactation on the same days as the weighing of litters.
17	Y	Each test g oup and control group should contain a sufficient number of mating pai s to yield approximately 20 pregnant females.
18	Y	Mating is c ne male to one female. Each female must be caged with a single randomly s elected male of the same dose until there is evidence of copulation (animals m ust then be separated) or either 3 estrous periods or 2 weeks has elapsed (ar imals should then be separated without further mating opportunit).
19	Not specified.	For mating the F1 offspring, at least one male and one female should be randomly s elected from each litter for mating with another pup of the same dose level ut from a different litter to produce the F2 generation.
20	Y	During pre nating and gestation, individual food consumption should be measured a t least weekly. Water consumption should also be measured weekly if t ne test substance is administered in water.
21	Two weeks.	Estrous cy le length and pattern evaluated by vaginal smears for all P and F1 fen ales during a minimum of 3 weeks prior to mating and through cohabitati n
22	Y	Each litter examined as soon as possible after delivery to establish number and sex of pups, stillbirths, live births and presence of gross anomalies. Pups found dea on day 0 should be examined for possible defects and cause of death
23	Y	Live pups sexed and weighed individually at birth or soon after, at least on days 4,7, 4, and 21 of lactation, at the time of vaginal patency or balanopre utial separation, and at termination.
24	NA	Age of v ginal opening and preputial separation determined for F1 weanlings selected for mating. If there is a treatment-related effect in F1 sex ratio or se ual maturation, anogenital distance should be measured on day 0 for all F2 ups.
25	Y	Standardi ation of litter sizes optional; if performed it should be on day 4 after birth by random selection to yield, as nearly as possible, 4M and 4F per litter or 5 M and 5F per litter. If sex ratio makes this impossible, partial adjustmer ts (such as 5M and 3F; or 4M and 6F) are acceptable; no adjustmer ts should be made on litters of 8 pups or less. SELECTIVE ELIMINA TION OF PUPS BASED ON BODY WEIGHT OR HEALTH IS NOT API ROPRIATE

26	Y	Individual litter observations
27	Y	All P and F1 adult males and females terminated when they are no longer needed for in-life assessment of reproductive effects. F1 offspring not selected for mating and all F2 offspring terminated
28	Y	Gross necropsy of all P and F1 adults, and (litter size permitting) at least 3 pups/sex/litter from unselected F1 weanlings and from F2 weanlings, with special attention to organs of reproductive system. Also, necropsy of dead pups and those sacrificed in a moribund condition
29	Y	At necropsy, a vaginal smear [from adult females] should be examined to determine the stage of the estrous cycle. The uteri of all cohabitated females should be examined for presence and number of implantation sites.
30	Y	For all P and F1 males at termination, sperm from one testis and one epididymis should be collected for enumeration of homogenization-resistant spermatids and cauda epididymal sperm reserves, respectively. Also, sperm from the cauda epididymis or vas deferens should be evaluated for motility and morphology. Evaluation of only control and high-dose males is acceptable, unless treatments are seen, mandating evaluation of lower dose groups.
31	Y	At the time of termination, the following organs of all P and F1 animals should be weighed: __x__ Ovaries __x__ Brain __x__ Kidneys __x__ Testes __x__ Pituitary __x__ Adrenal glands __x__ Prostate __x__ Liver __x__ Spleen __x__ Uterus (with oviducts and cervix) __x__ Known target organs __x__ Epididymides (total weights for both and cauda weight for either one or both Seminal vesicles (with coagulating glands and their fluids)
32	Y	For F1 and F2 weanlings that are examined in gross necropsy, the following organs should be weighed from at least one randomly selected pup/sex/litter: __x__ Brain __x__ Spleen __x__ Thymus
33	Y	The following organs and tissues from P and F1 animals should be fixed and stored in a suitable medium for histopathological examination: __x__ Vagina __x__ Seminal vesicles __x__ Adrenals __x__ Uterus __x__ Prostate __x__ Target organs (with oviducts and cervix) _____ Abnormal tissue __x__ Ovaries __x__ Coagulating gland __x__ One testis __x__ Pituitary __x__ One epididymis

34	Y	Full histop: thology of the organs listed in #33 above from 10 randomly chosen hig dose and control P and F1 animals per sex; organs showing dose-related cha ges should be examined from remaining high-dose and control animals, as well as from all animals in low- and mid-dose groups. Also, histopathol)gy should be done on reproductive organs from all animals with no or low f :rtility.
35	Y	Quantitativ : evaluation of primordial follicles and small growing follicles from the o' aries of F1 females
36	Y	Preservati n of grossly abnormal tissue and target organs (if known) from F1 and F2 we: nlings selected for gross necropsy
37	Y	Historical ontrol data [usually from the performing laboratory], including dates of st dies, strain and source of animals, and the vehicle(s) and route(s) of admini: tration, when appropriate to enhance the interpretation of the study findings.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246334

870.3800 Reproduction and Fertility Effects

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study conducted under GLP (with statement
2	Y	Technical form of the active ingredient used.
3	Y Expiration date.	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study.
4	Y	Analyses for test material stability, homogeneity and concentration in dosing medium
5	Y	Preferred species is rat; if another species is used, justification is needed.
6	Y	Identification as to test animal strain and source; strains with low fecundity should not be used.
7	Y	Parental (P) animals should be 5 to 9 weeks old at the start of dosing.
8	Y	Normally (except when a limit dose of 1000 mg/kg/day or 20,000 ppm in the diet shows no effects) there should be three dose levels and a concurrent control. Dose levels should be spaced to produce a gradation of toxic effects
9	Y	At the highest dose level, there should be some reproductive and/or systemic toxicity (but mortality should not exceed 10%), or a limit dose should be achieved (1000 mg/kg/day, or 20,000 ppm in the diet)
10	Y	The lowest dose level should not produce any evidence of either systemic or reproductive toxicity
11	Y	Test substance is usually administered by the oral route (diet, drinking water, or gavage). If another route is used, justification must be provided.
12	Y	Dosage must be on a 7-days-a-week basis.
13	Y	At least two generations are bred.
14	Y	Individual daily observations, with thorough weekly physical examinations
15	Y	Daily dosing of the P and F1 males and females should continue until termination

16	Y	P and F1 ai imals should be individually weighed on the first day of dosing and weekly thereafter. Parental females (P and F1) should be weighed on approximai ely gestation days 0, 7, 14 and 21, and during lactation on the same days as the weighing of litters.
17	Y	Each test g oup and control group should contain a sufficient number of mating pai s to yield approximately 20 pregnant females.
18	Y	Mating is c ne male to one female. Each female must be caged with a single randomly s elected male of the same dose until there is evidence of copulation (animals m ust then be separated) or either 3 estrous periods or 2 weeks has elapsed (ar imals should then be separated without further mating opportunit).
19	Y	For mating the F1 offspring, at least one male and one female should be randomly s elected from each litter for mating with another pup of the same dose level ut from a different litter to produce the F2 generation.
20	Y	During pre nating and gestation, individual food consumption should be measured : t least weekly. Water consumption should also be measured weekly if t ne test substance is administered in water.
21	Y	Estrous cy le length and pattern evaluated by vaginal smears for all P and F1 fer ales during a minimum of 3 weeks prior to mating and through cohabitati n
22	Y	Each litter examined as soon as possible after delivery to establish number and sex of pups, stillbirths, live births and presence of gross anomalies. Pups found dea . on day 0 should be examined for possible defects and cause of death
23	Y	Live pups sexed and weighed individually at birth or soon after, at least on days 4,7, 4, and 21 of lactation, at the time of vaginal patency or balanopre utial separation, and at termination.
24	Y	Age of v ginal opening and preputial separation determined for F1 weanlings selected for mating. If there is a treatment-related effect in F1 sex ratio or se cual maturation, anogenital distance should be measured on day 0 for all F2 ups.
25	Y	Standardi ation of litter sizes optional; if performed it should be on day 4 after birth by random selection to yield, as nearly as possible, 4M and 4F per litter or 5 M and 5F per litter. If sex ratio makes this impossible, partial adjustmer ts (such as 5M and 3F; or 4M and 6F) are acceptable; no adjustmer ts should be made on litters of 8 pups or less. SELECTIVE ELIMIN/ TION OF PUPS BASED ON BODY WEIGHT OR HEALTH IS NOT API ROPRIATE

26	Y	Individual litter observations
27	Y	All P and F1 adult males and females terminated when they are no longer needed for in-life assessment of reproductive effects. F1 offspring not selected for mating and all F2 offspring terminated
28	Y	Gross necropsy of all P and F1 adults, and (litter size permitting) at least 3 pups/sex/litter from unselected F1 weanlings and from F2 weanlings, with special attention to organs of reproductive system. Also, necropsy of dead pups and those sacrificed in a moribund condition
29	Y	At necropsy, a vaginal smear [from adult females] should be examined to determine the stage of the estrous cycle. The uteri of all cohabitated females should be examined for presence and number of implantation sites.
30	Y	For all P and F1 males at termination, sperm from one testis and one epididymis should be collected for enumeration of homogenization-resistant spermatids and cauda epididymal sperm reserves, respectively. Also, sperm from the cauda epididymis or vas deferens should be evaluated for motility and morphology. Evaluation of only control and high-dose males is acceptable, unless treatments are seen, mandating evaluation of lower dose groups.
31	Y	At the time of termination, the following organs of all P and F1 animals should be weighed: __X__ Ovaries __X__ Brain __X__ Kidneys __X__ Testes __X__ Pituitary __X__ Adrenal glands __X__ Prostate __X__ Liver __X__ Spleen __X__ Uterus (with oviducts and cervix) ____ Known target organs ____ Epididymides (total weights for both and cauda weight for either one or both) Seminal vesicles (with coagulating glands and their fluids
32	Y	For F1 and F2 weanlings that are examined in gross necropsy, the following organs should be weighed from at least one randomly selected pup/sex/litter: __X__ Brain __X__ Spleen __X__ Thymus
33	Y	The following organs and tissues from P and F1 animals should be fixed and stored in a suitable medium for histopathological examination: __X__ Vagine __X__ Seminal vesicles __X__ Adrenals __X__ Uterus (with oviducts and cervix) _____ Target organs __X__ Ovaries __X__ Prostate _____Abnormal tissues __X__ One testis __X__ Coagulating gland __X__ One epididymis __X__ Pituitary

34	Y	Full histop thology of the organs listed in #33 above from 10 randomly chosen hig . dose and control P and F1 animals per sex; organs showing dose-related cha ıges should be examined from remaining high-dose and control animals, as well as from all animals in low- and mid-dose groups. Also, histopathol ɔgy should be done on reproductive organs from all animals with no or low f ɔrtility.
35	Y	Quantitativ ɔ evaluation of primordial follicles and small growing follicles from the o aries of F1 females
36	Y	Preservati ɔn of grossly abnormal tissue and target organs (if known) from F1 and F2 we nlings selected for gross necropsy
37	Y	Historical ontrol data [usually from the performing laboratory], including dates of st dies, strain and source of animals, and the vehicle(s) and route(s) of admini tration, when appropriate to enhance the interpretation of the study findings.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246335

870.4100a Chronic Oral Toxicity - Rodent -Rat

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement
2	Y	Technical form of the active ingredient used.
3	Y	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4	Y	Rat is preferred. If another species is used, then justification should be provided.
5	Y	Identification as to test animal strain and source.
6	Y	Age at start of dosing for rat: 8-9 wks.
7	Y	20 animals/sex/dose level, with concurrent control group. Usually 3 dose levels, but if testing at 1000 mg/kg/day shows no effects, then this is adequate.
8	N/A	If interim sacrifices, number of animals/group increased accordingly
9	Y	Dosage by gavage or with capsules for 5 days/week is acceptable; if via drinking water or feed, then 7 days/week **Gavage**
10	Y	Dosage should be for at least 12 months.
11	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.
12	Y	Lowest dose level is a NOAEL.
13	Y	Highest dose level produces toxicity or is a limit dose (1000 mg/kg/day
14	Y	Individual daily observations (includes 2X/day for morbidity and mortality
15	Y	Individual clinical exams prior to initiation and at least once weekly thereafter **and open field - weeks: FOB - 6/12 months.**
16	Y	Individual body weights (before administration, once a week for the first 13 weeks of the study, and at least once every 4 weeks thereafter).

17	Y	Food consu iption (individual or cage) should be measured on a weekly basis for the first 3 weeks of the study, and at approximately monthly intervals thereafter.M easurements of water consumption should also be determined for the same int rvals if the test substance is administered in the drinking water.
18	N	Assessment of motor activity, grip strength, reactivity to sensory stimuli (near the end of e posure period, and not earlier than month 11).
19	Y	Ophthalmos copic examination on all animals prior to initiation of dosage, and on at least 1) rodents/sex in high dose and control groups at termination; if changes in t ie eyes are observed, all animals should be examined
20	Y	Hematology and clinical chemistry, and urinalysis on at least 10/sex/dose group at app roximately 6 month intervals and at termination
21	Y	**Hematolog (Hemo/Clinical Chemistry/Urinology: Weeks: 14, 27, 54 and 53.)** __X__ E ythrocyte count __X__ H matocrit __X__ M ean corpuscualr volume __X__ M ean corpuscular hemoglobin __X__ M ean corpuscualr hemoglobin concentration __X__ D fferential count __X__ P atelet count __X__ P othrombin time or activated partial thromboplastin time. __X__ Leukocyte count __X__ Hemoglobin concentration
22	Y	**Clinical C iemistry** __x__ Po assium __x__ So lium __x__ Ca cium __x__ Ph osphorus __x__ Gl ucose __x__ Al anine aminotransferase __x__ As partate aminotransferase __x__ Al kaline phosphatase _____ So bitol dehydrogenase _____ Ga mma glutamyl transpep. _____ Ch olinesterases _____ Ho rmones _____ M themoglobin __x__ Fa sting triglycerides __x__ Total cholesterol __x__ Total protein __x__ Albumin __x__ Urea nitrogen __x__ Creatinine __x__ T_3 __x__ T_4 __x__ TSH Measurem nt that should be made if test material is known or suspected of affecting th is or a related parameter. Activity of more than two of these hepatic enzymes should be measured.

23	Y	**Urinalysis,** using timed urine volume collection. __X__ Appearance __X__ pH __X__ Glucose __X__ Volume __X__ Protein __X__ Blood or blood cells __X__ Osmolality or specific gravity
24	Y	Individual gross necropsy of all animals
25	Y	**Organ weights** (weighed wet as soon as possible after dissection). __x__ Liver __x__ Epididymides _____ Thymus __x__ Kidneys __x__ Ovaries __x__ Spleen __x__ Adrenals __x__ Uterus __x__ Brain __x__ Testes __x__ Heart

26	Y	Preservation of the following tissues, with full histopathology from all control and high-dose animals (extension to all dosage groups if treatment-related changes are observed in the high-dose group) and from all animals that died or were killed during the study, along with gross lesions and target tissues in all animals. X adrenals X aorta X bone marrow X brain (3 regions) X salivary glands X cecum X colon X duodenum X epididymides X esophagus X eyes (with retina X heart X ileum X jejunum X kidneys X larynx X liver X lungs X lymph nodes X mammary gland (F) X musculature§ X nose X ovaries X oviduct§ X pancreas X pituitary X prostate X rectum X seminal vesicle(s) X skin (treated and adjacent untreated) X spinal cord (3X) X spleen X stomach X testes X thymus X thyroid X trachea X urinary bladder X uterus X vagina X Zymbol gland X All tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246336

870.4100b Chronic Oral Toxicity - Non Rodent -Dog

Does this study meet the following acceptance criteria?

1	Y	Study conducted under GLP (with statement).
2	Y	Technical form of the active ingredient used.
3	Y	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date, vehicle used if any). It is preferable to use one lot throughout the study.
4	Y	Dog is preferred. If another species is used, then justification should be provided
5	Y	Identification as to test animal strain and source
6	Y	Age at start of dosing for dog: between 4 and 6 months; no later than 9 months.
7	Y	4 animals/sex/dose level, with concurrent control group. Usually 3 dose levels, but if testing at 1000 mg/kg/day shows no effects, then this is adequate.
8	N/A	If interim sacrifices, number of animals/group increased accordingly.
9	Y	Dosage by gavage or with capsules for 5 days/week is acceptable; if via drinking water or feed, then 7 days/week. **Gavage**
10	Y	Dosage should be for at least 12 months.
11	Y	Dogs are caged separately (recommended).
12	Y	Analyses for test material stability, homogeneity entration in dosing medium.
13	Y	Lowest dose level is a NOAEL.
14	Y	Highest dose level produces toxicity or is a limit dose (1000 mg/kg/day).
15	Y	Individual daily observations (includes 2X/day for morbidity and mortality).
16	Y	Individual clinical exams prior to initiation and at least once weekly thereafter **and neurotox**.
17	Y	Individual body weights (before administration, once a week for the first 13 weeks of the study, and at least once every 4 weeks thereafter).
18	Y	Individual food consumption should be measured on a weekly basis for the first 13 weeks of the study, and at approximately monthly intervals thereafter.Measurements of water consumption should also be determined for the same intervals if the test substance is

		administered in the dr nking water.
19	Y	Ophthalmoscopic exa nination on all animals prior to initiation of dosage, and on all animals of high dose a nd control groups at termination; if changes in the eyes are observed, all animals should be :xamined.
20	Y	Hematology, clinical hemistry and urinalysis on all animals at least once prior to initiation of treatment, at 6 mor h intervals during exposure, and at termination
21	Y	X Erythrocyte c ount X Mean corp. volume X Leukocyte count X Hemoglobin :onc. X Mean corp. hemogl . X Differential count X Hematocrit X Mean corp. hem. con. X Platelet count X Prothrombir time or activated partial thromboplastin time
22	Y	**Clinical Chemistry** X Potassium X Total cholestero1 X T_3 X Sodium X Urea nitrogen X T_4 X Calcium X Total protein X TSH X Phosphorus X Total bilirubin X UDP X Chloride X Glucose X Cytochrome P-450 X Albumin X Alanine ami otransferase X Aspartate a iinotransferase X Alkaline ph sphatase X Creatinine ____ Sorbitol del ydrogenase X Gamma glu amyl transpep. -- Cholinester ses X Hormones ____ Methemogl bin X Fasting trig ycerides Measurement that sh uld be made if test material is known or suspected of affecting this or a related parameter. Activity of more tha two of these hepatic enzymes should be measured.
23		**Urinalysis,** perform d using timed urine volume collection. X Appearanc X pH X Glucose X Volume X Protein X Blood or bl od cells X Osmolality or specific gravity
24		Individual gross nec opsy of all animals.
25	Y	**Organ weights** (wei ghed wet as soon as possible after dissection). X Liver X Testes X Lungs X Heart X Kidneys X Pituitary X Epididymi es X Spleen X Thymus X Adrenals X Ovaries X Brain X Thyroid (w th parathyroid) X Uterus

26	Y	Preservation of the following tissues, with full histopathology from all control and high-dose animals (extension to all dosage groups if treatment-related changes are observed in the high-dose group) and from all animals that died or were killed during the study, along with gross lesions and target tissues in all animals __X__ adrenals __X__ aorta __X__ bone marrow __X__ brain (3 regions) __X__ salivary glands __X__ cecum __X__ colon _____ duodenum __X__ epididymides __X__ esophagus __X__ eyes (with retina __X__ heart __X__ ileum __X__ jejunum __X__ kidneys __X__ larynx __X__ liver __X__ lungs __X__ lymph nodes __X__ mammary gland (F) __X__ musculature __X__ nose __X__ ovaries _____ oviduct __X__ pancreas __X__ pituitary __X__ prostate __X__ rectum __X__ seminal vesicle(s) __X__ skin (treated and adjacent untreated) __X__ spinal cord (3X) __X__ spleen __X__ stomach __X__ testes __X__ thymus __X__ thyroid __X__ trachea __X__ urinary bladder __X__ uterus __X__ vagina __X__ Zymbol gland __X__ All tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246337

870.4100b C ronic Oral Toxicity - Non Rodent -Dog - Diet

Does this study meet the following acceptance criteria?

1	Y	Study conducted nder GLP (with statement).
2	Y	Technical form c the active ingredient used.
3	Y	Full identificatio of the test material (chemical identification, percentage active, batch or lot number, ph ysical properties, purity/impurities, expiration date, vehicle used if any). It is prefer ble to use one lot throughout the study.
4	Y	Dog is preferred. If another species is used, then justification should be provided
5	Y	Identification as o test animal strain and source
6	Y	Age at start of d sing for dog: between 4 and 6 months; no later than 9 months.
7	Y	4 animals/sex/dc se level, with concurrent control group. Usually 3 dose levels, but if testing at 1000 n g/kg/day shows no effects, then this is adequate.
8	N/A	If interim sacrifi es, number of animals/group increased accordingly.
9	Y	Dosage by gava e or with capsules for 5 days/week is acceptable; if via drinking water or feed, then 7 d ys/week.
10	No	Dosage should b for at least 12 months. 30 wks only. ***Rationale For L ess Than* 1 *Year Exposure.* Page 19 of the Study Report: "Since the developmer t of the test compound was discontinued, the study was also discontinued."** **JR. NOTE: Ho vever, a 1-year study with the parent JAU 6476 is available (MRID 46246336) JR. 6/18/04.**
11		Dogs are caged separately (recommended).
12	Y	Analyses for tes material stability, homogeneity entration in dosing medium.
13	Y	Lowest dose lev el is a NOAEL.
14	Y	Highest dose le el produces toxicity or is a limit dose (1000 mg/kg/day).
15	Y	Individual daily observations (includes 2X/day for morbidity and mortality).
16	Y	Individual clini al exams prior to initiation and at least once weekly thereafter.
17	Y	Individual body weights (before administration, once a week for the first 13 weeks of the study, and a least once every 4 weeks thereafter).

18	Y	Individual food consumption should be measured on a weekly basis for the first 13 weeks of the study, and at approximately monthly intervals thereafter.Measurements of water consumption should also be determined for the same intervals if the test substance is administered in the drinking water.
19	Y	Ophthalmoscopic examination on all animals prior to initiation of dosage, and on all animals of high dose and control groups at termination; if changes in the eyes are observed, all animals should be examined.
20	Y	Hematology, clinical chemistry and urinalysis on all animals at least once prior to initiation of treatment, at 6 month intervals during exposure, and at termination. **Hematology: Week: 2: 1, 5, 12, 20, 25.** **Clinical Chemistry** **Urinanalysis: Week 2: 1, 5, 12, 25, 30.**
21	Y	**Hematology** __x__ Erythrocyte count __x__ Mean corp. volume _____ Leukocyte count __x__ Hemoglobin conc. __x__ Mean corp. hemogl. _____ Differential count __x__ Hematocrit __x__ Mean corp. hem. con. __x__ Platelet count __x__ Prothrombin time or activated partial thromboplastin time

22	Y	**Clinical Chemis ry** __x__ Potassiu n __x__ Sodium __x__ Calcium __x__ Phospho us __x__ Chloride __x__ Albumi __x__ Alanine aminotransferase __x__ Aspartat aminotransferase __x__ Alkaline phosphatase __x__ Creatini e __x__ Sorbitol dehydrogenase __x__ Gamma glutamyl transpep. __x__ Choline terases __x__ Hormor es __x__ Methem globin __x__ Fasting riglycerides __x__ Total cholesterol __x__ Urea nitrogen __x__ Total protein __x__ Total bilirubin __x__ Glucose __x__ T_3 __x__ T_4 __x__ TSH Measurement tha t should be made if test material is known or suspected of affecting this or a related p arameter. Activity of more than two of these hepatic enzymes should be measured.
23	Y	**Urinalysis,** perfo rmed using timed urine volume collection. __x__ Appeara ice __x__ pH __x__ Glucose __x__ Volume __x__ Protein __x__ Blood o blood cells __x__ Osmolal ty or specific gravity
24		Individual gross necropsy of all animals.
25		**Organ weights** weighed wet as soon as possible after dissection). __x__ Liver __x__ Testes __x__ Lungs __x__ Heart __x__ Kidneys __x__ Pituitary __-__ Epididyn ides __x__ Spleen __x__ Pancreas __x__ Adrenal __x__ Ovaries __x__ Brain __x__ Thyroid (with parathyroid) __x__ Uterus

26	Y	Preservation of the following tissues, with full histopathology from all control and high-dose animals (extension to all dosage groups if treatment-related changes are observed in the high-dose group) and from all animals that died or were killed during the study, along with gross lesions and target tissues in all animals __x__ adrenals __x__ aorta __x__ bone marrow __x__ brain (3 regions) __x__ salivary glands __x__ cecum __x__ colon __x__ duodenum __x__ epididymides __x__ esophagus __x__ eyes (with retina __x__ heart __x__ ileum __x__ jejunum __x__ kidneys __x__ larynx __x__ liver __x__ lungs __x__ lymph nodes __x__ mammary gland (F) __x__ musculature __x__ nose __x__ ovaries __x__ oviduct __x__ pancreas __x__ pituitary __x__ prostate __x__ rectum __x__ seminal vesicle(s) __x__ skin (treated and adjacent untreated) __x__ spinal cord (3X) __x__ spleen __x__ stomach __x__ testes __x__ thymus __x__ thyroid __x__ trachea __x__ urinary bladder __x__ uterus __x__ vagina __x__ Zymbol gland __x__ All tissue with abnormalities.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246338

870 4200a Carcingenicity - Rat -Gavage

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study con lucted under GLP (with statement).
2	Y	Technical form of the active ingredient used.
3	Y	Full ident fication of the test material (chemical identification, percentage active, batch or l t number, physical properties, purity/impurities, expiration date, vehicle us d, if any). It is preferable to use one lot throughout the study
4	Y	Rat or mo se is preferred; another mammalian species requires justification.
5	Y	Identifica ion as to test animal strain and source.
6	Y	Age at sta t of dosing: no later than 8 weeks of age.
7	Y	50 animal s/sex/dose level, with concurrent control group.
8	Y	If interim sacrifices, number of animals/group increased accordingly
9	Y	Three dos e levels; highest should cause toxicity but not significantly alter life span, or (lternatively) be a limit dose of 1000 mg/kg/day.
10	Y	Highest (ose determined from findings from a 90-day study
11	Y	Lowest d se should produce no evidence of toxicity.
12	Y	Survival n any group should not go below 50 percent at 15 months in mice and 18 month s in rats, and not below 25 percent at 18 months in mice and 24 months in rats.
13	Y	Dosage b / gavage or with capsules for 5 days/week is acceptable; if via drinking water or eed, then 7 days/week.
14	Y	Dosage n ust be for at least 18 months for mice and hamsters, 24 months for rat.
15	Y	Periodic nalyses for test material stability, homogeneity and concentration in dosing m edium
16	Y	Individu l daily observations (includes 2X/day for morbidity and mortality).
17	Y	Individu l clinical exams prior to initiation and at least once weekly thereafter.

18	Y	Individual body weights made before administration, once a week for the first 13 weeks of the study, and at least once every 4 weeks thereafter.
19	Y	Food consumption (individual or cage) should be measured on a weekly basis for the first 13 weeks of the study, and at approximately monthly intervals thereafter. Measurements of water consumption should also be determined for the same intervals if the test substance is administered in the drinking water.
20	Y	Blood smears obtained from all animals at 12 months, 18 months and at terminal sacrifice, with differential performed on smears from high-dose and controls at terminal sacrifice. If there are differences between these groups, then 12- and 18- month smears should also be examined as well as those from lower-dose groups. **Additionally, Standard Hematology & Hormones (T3 , T4 , TSH) & Urinanalysis parameters were evaluated at weeks: 53, 79 and 105.**
21	Y	Individual gross necropsy for all animals.
22	Y	**Organ weights** (weighed wet as soon as possible after dissection). __x__ Liver __x__ Testes __x__ Heart __x__ Kidneys __x__ Epididymides __x__ Spleen __x__ Adrenals __x__ Ovaries __x__ Brain __x__ Uterus

23	Y	Preservati n of the following tissues, with full histopathology from all control and thigh- lose animals (extension to all dosage groups if treatment-related changes ar e observed in the high-dose group) and from all animals that died or were kille during the study, along with gross lesions and target organs in all animals. __x__ a renals __x__ a rta __x__ b ne marrow __x__ b ain (3 regions) __x__ s livary glands __x__ c cum __x__ c lon __x__ d uodenum __x__ e ididymides __x__ e ophagus __x__ e es (with retina) __x__ h art __x__ i eum __x__ j junum __x__ k dneys __x__ l rynx __x__ l ver __x__ l ngs __x__ l mph nodes __x__ m ammary gland (F) __x__ m usculature __x__ n ose __x__ o varies __x__ o viduct __x__ p ancreas __x__ p ituitary __x__ p rostate __x__ r ectum __x__ s eminal vesicle(s) __x__ s kin (treated and a djacent untreated) __x__ s pinal cord (3X) __x__ s pleen __x__ s tomach __x__ testes __x__ thymus __x__ thyroid __x__ trachea __x__ urinary bladder __x__ uterus __x__ vagina __x__ Zymbol gland __x__ All tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246339

870.4200b Carcingenicity - Mice -Gavage

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study conducted under GLP (with statement).
2	Y	Technical form of the active ingredient used.
3	Y	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study
4	Y	Rat or mouse is preferred; another mammalian species requires justification.
5	Y	Identification as to test animal strain and source.
6	Y	Age at start of dosing: no later than 8 weeks of age.
7	Y	50 animals/sex/dose level, with concurrent control group.
8	N/A	If interim sacrifices, number of animals/group increased accordingly
9	Y	Three dose levels; highest should cause toxicity but not significantly alter life span, or (alternatively) be a limit dose of 1000 mg/kg/day.
10	Y	Highest dose determined from findings from a 90-day study
11	Y	Lowest dose should produce no evidence of toxicity.
12	Y	Survival in any group should not go below 50 percent at 15 months in mice and 18 months in rats, and not below 25 percent at 18 months in mice and 24 months in rats.
13	Y	Dosage by gavage or with capsules for 5 days/week is acceptable; if via drinking water or feed, then 7 days/week.
14	Y	Dosage must be for at least 18 months for mice and hamsters, 24 months for rat.
15	Y	Periodic analyses for test material stability, homogeneity and concentration in dosing medium
16	Y	Individual daily observations (includes 2X/day for morbidity and mortality).
17	Y	Individual clinical exams prior to initiation and at least once weekly thereafter.
18	Y	Individual body weights made before administration, once a week for the first 13 weeks of the study, and at least once every 4 weeks thereafter.

19	Y	Food cons mption (individual or cage) should be measured on a weekly basis for the first 1: weeks of the study, and at approximately monthly intervals thereafter. Measurements of water consumption should also be determined for the same i ntervals if the test substance is administered in the drinking water.
20	Y	Blood sm ears obtained from all animals at 12 months, 18 months and at terminal s crifice, with differential performed on smears from high-dose and controls a terminal sacrifice. If there are differences between these groups, then 12- and 1{ - month smears should also be examined as well as those from lower-dose grou s. **In additic n: Differential, esophogle and morphology were evaluated at week 78 (contr l and high dose).**
21	Y	Individua gross necropsy for all animals.
22	Y	**Organ w ights** (weighed wet as soon as possible after dissection). __x__ I iver __x__ Testes __x__ Heart __x__ K idneys __x__ Epididymides __x__ Spleen __x__ A drenals __x__ Ovaries __x__ Brain __x__ U terus

23	Y	Preservation of the following tissues, with full histopathology from all control and thigh-dose animals (extension to all dosage groups if treatment-related changes are observed in the high-dose group) and from all animals that died or were killed during the study, along with gross lesions and target organs in all animals. __x__ adrenals __x__ aorta __x__ bone marrow __x__ brain (3 regions) __x__ salivary glands __x__ cecum __x__ colon __x__ duodenum __x__ epididymides __x__ esophagus __x__ eyes (with retina) __x__ heart __x__ ileum __x__ jejunum __x__ kidneys __x__ larynx __x__ liver __x__ lungs __x__ lymph nodes __x__ mammary gland (F) __x__ musculature __x__ nose __x__ ovaries __x__ oviduct§ __x__ pancreas __x__ pituitary __x__ prostate __x__ rectum __x__ seminal vesicle(s) __x__ skin (treated and adjacent untreated) __x__ spinal cord (3X) __x__ spleen __x__ stomach __x__ testes __x__ thymus __x__ thyroid __x__ trachea __x__ urinary bladder __x__ uterus __x__ vagina __x__ Zymbol gland __x__ All tissues with abnormalities.

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246340

870.4200b Carcingenicity - Mice -Dietary

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study con lucted under GLP (with statement).
2	Y	Technical form of the active ingredient used.Y
3	Y	Full ident fication of the test material (chemical identification, percentage active, batch or l t number, physical properties, purity/impurities, expiration date, vehicle us ed, if any). It is preferable to use one lot throughout the study
4	Y	Rat or mc use is preferred; another mammalian species requires justification.
5	Y	Identifica ion as to test animal strain and source.
6	Y	Age at sta rt of dosing: no later than 8 weeks of age.
7	Y	50 anima s/sex/dose level, with concurrent control group.
8	Y	If interim sacrifices, number of animals/group increased accordingly
9	Y	Three do e levels; highest should cause toxicity but not significantly alter life span, or (lternatively) be a limit dose of 1000 mg/kg/day.
10	Y	Highest ose determined from findings from a 90-day study
11	Y	Lowest ose should produce no evidence of toxicity.
12	Y	Survival n any group should not go below 50 percent at 15 months in mice and 18 month s in rats, and not below 25 percent at 18 months in mice and 24 months in rats.
13	Y	Dosage b gavage or with capsules for 5 days/week is acceptable; if via drinking water or eed, then 7 days/week.
14	Y	Dosage r ust be for at least 18 months for mice and hamsters, 24 months for rat.
15	Y	Periodic nalyses for test material stability, homogeneity and concentration in dosing m edium
16	Y	Individu l daily observations (includes 2X/day for morbidity and mortality).
17	Y	Individu l clinical exams prior to initiation and at least once weekly thereafter.
18	Y	Individu l body weights made before administration, once a week for the first 13 weeks o the study, and at least once every 4 weeks thereafter.

19	Y	Food consumption (individual or cage) should be measured on a weekly basis for the first 13 weeks of the study, and at approximately monthly intervals thereafter. Measurements of water consumption should also be determined for the same intervals if the test substance is administered in the drinking water.
20	Y	Blood smears obtained from all animals at 12 months, 18 months and at terminal sacrifice, with differential performed on smears from high-dose and controls at terminal sacrifice. If there are differences between these groups, then 12- and 18- month smears should also be examined as well as those from lower-dose groups. **Standard Hematological and Clinical parameters were evaluated at weeks 51, 79 and 103 (Hematological), 51 and 105 (Clinical Chemistry)**
21	Y	Individual gross necropsy for all animals.
22	Y	**Organ weights** (weighed wet as soon as possible after dissection). x Liver — x Testes — x Heart x Kidneys — x Epididymides — x Spleen _____ Adrenals — x Ovaries — x Brain _____ Uterus — x Lungs

23	Y	Preservati n of the following tissues, with full histopathology from all control and thigh- lose animals (extension to all dosage groups if treatment-related changes a : observed in the high-dose group) and from all animals that died or were kille during the study, along with gross lesions and target organs in all animals. __x__ ad enals __x__ ao ta _____ bo e marrow _____ br in (3 regions) _____ sal vary glands _____ ce um _____ co on _____ du denum _____ ep didymides _____ es phagus _____ ey s (with retina _____ he rt _____ ile m _____ je num _____ ki lneys _____ la ynx _____ li er _____ lu gs _____ ly nph nodes _____ m mmary gland (F) _____ m sculature _____ n se _____ o aries _____ o iduct§ _____ p ncreas _____ pi uitary _____ pr state _____ re tum _____ se minal vesicle(s) _____ sk in (treated and ad jacent untreated) _____ sp inal cord (3X) _____ sp leen _____ st mach __x__ testes __x__ thymus __x__ thyroid __x__ trachea __x__ urinary bladder __x__ uterus __x__ vagina __x__ Zymbold gland __x__ All tissues with

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246342

870.4300 Combined Chronic Oral Toxicity/Carcingenicity - Rat -Dietary

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study conducted under GLP (with statement
2	Y	Technical form of the active ingredient used.
3	Y	Full identification of the test material (chemical identification, percentage active, atch or lot number, physical properties, purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study.
4	Y	For the oral route, the rat is preferred. If another species is used, then justification should be provided
5	Y	Identification as to test animal strain and source
6	Y	Age at start of dosing for rat: no later than 8 weeks.
7	Y	50 animals/sex/dose level, with concurrent control group. Usually 3 dose levels, but if testing at 1000 mg/kg/day shows no effects, then this may be adequate.
8	Y	At least 10 additional animals/sex/dose level should be used for satellite dose groups and the satellite control group (with sacrifice at 12 months) to allow for the evaluation of chronic toxicity after 12 months.
9	Y	Dosage by gavage or with capsules for 5 days/week is acceptable; if via drinking water or feed, then 7 days/week. **In Diet**
10	Y	Dosage should be for at least 24 months for rats (18 months for mice), and not longer than 30 months for rats (24 months for mice).
11	Y	Analyses for test material stability, homogeneity and concentration in dosing medium.

12	Y	Highest dc se level produces toxicity without substantially altering the normal life span d ıe to effects other than tumors, or is a limit dose (1000 mg/kg/day). **Doses wei e selected based on the 28-day and 25-day feeding studies. Since the 90-da' study [MRID No. 46246309] was initiated in 1992 <u>after</u> the inihibitio . and the combination study [1990].** **<u>28-Day</u>: 0, 100, 300, 1000 ppm** **<u>25-Day</u>: 0, 1500, 2500, 500 ppm** **NOAEL: 1000 ppm and above** **.500 ppm and above** **BWG.** **14% ÷ 31 9 ÷ ♀ - 1500 ppm** **33% ÷ 31 12 ÷ ♀ - 2500 ppm** **Lc thal: 5000 ppm** **All died.** **☒ Liver weights - D.R. Absolute/Relative ♂/♀** **☒ Liver enzymes.** **Histopathological - Liver: *100 - 300 - 1000* ppm.** **- 300 and 1000 ppm** **Doses: Sc lected for Combination: 20, 140, 980 ppm.**
13	Y	Highest d ›se determined from findings from a 90-day study.
14	Y	Lowest d ›se level is a NOEL.
15	Y	Individua . daily observations (includes 2X/day for morbidity and mortality).
16	Y	Individua . clinical exams prior to initiation and at least once weekly afterwards outside tl e home cage.
17	Y	Individua l body weights (before administration, once a week for the first 13 weeks of the study, and at least once every 4 weeks thereafter).
18	Y	Food cor sumption (individual or cage) should be measured on a weekly basis for the first 1 3 weeks of the study, and at approximately monthly intervals thereafte . Measurements of water consumption should also be determined for the same intervals if the test substance is administered in the drinking water.

19	N	Assessment of motor activity, grip strength, reactivity to sensory stimuli (near the end of the first year of the exposure period, and not earlier than month 11).
20	Y	Ophthalmoscopic examination on all animals prior to initiation of dosage, and on at least 10 rodents/sex in high dose and control groups at termination; if changes in the eyes are observed, all animals should be examined.
21	Y	Hematology and clinical chemistry, and urinalysis on at least 10/sex/dose group at approximately 6 month intervals and at one year (also at 3 months if effects were observed in a preliminary subchronic study).
22	Y	**Hematology** __x__ Erythrocyte count __x__ Leukocyte count __x__ Hemoglobin concentration. __x__ Hematocrit __x__ Mean corpuscular volume __x__ Mean corpuscular hemoglobin __x__ Mean corpuscular hemoglobin concentration. __x__ Differential count __x__ Platelet count __x__ Prothrombin time or activated partial thromboplastin time
23	Y	**Clinical Chemistry** __x__ Potassium __x__ Total cholesterol __x__ T_3 __x__ Sodium __x__ Urea nitrogen __x__ T_4 __x__ Calcium __x__ Phosphorus __x__ Glucose __x__ Albumin __x__ Alanine aminotransferase __x__ Aspartate aminotransferase __x__ Alkaline phosphatase _____ Sorbitol dehydrogenase __x__ Creatinine __x__ Total protein __x__ Gamma glutamyl transpep. _____ Cholinesterases __x__ Hormones _____ Methemoglobin __x__ Fasting triglycerides Measurement that should be made if test material is known or suspected of affecting this or a related parameter. Activity of more than two of these hepatic enzymes should be measured

24	Y	**Urinalysis**, using timed urine volume collection, at the end of the first year. __x__ Appearance __x__ pH __x__ Glucose __x__ Volume __x__ Protein __x__ Blood or blood cells __x__ Osmolality or specific gravity
25	Y	Individual gross necropsy of all animals.
26	Y	**Organ weights** (weighed wet as soon as possible after dissection). __x__ Liver __x__ Epididymides __x__ Heart __x__ Kidneys __x__ Ovaries __x__ Spleen __x__ Adrenals _____ Uterus __x__ Brain __x__ Testes __x__ Lungs

27	Y	Preservation of the following tissues, with full histopathology from all control and high-dose animals (extension to all dosage groups if treatment-related changes are observed in the high-dose group) and from all animals that died or were killed during the study, along with gross lesions and target tissues in all animals. __x__ adrenals __x__ aorta __x__ bone marrow __x__ brain (3 regions) __x__ salivary glands __x__ cecum __x__ colon __x__ duodenum __x__ epididymides __x__ esophagus __x__ eyes (with retina __x__ heart __x__ ileum __x__ jejunum __x__ kidneys __x__ larynx __x__ liver __x__ lungs __x__ lymph nodes __x__ mammary gland (F) __x__ musculature __x__ nose __x__ ovaries __x__ oviduct§ __x__ pancreas __x__ pituitary __x__ prostate __x__ rectum __x__ seminal vesicle(s) __x__ skin (treated and adjacent untreated) __x__ spinal cord (3X) __x__ spleen __x__ stomach __x__ testes __x__ thymus __x__ trachea __x__ uninary bladder __x__ uterus __x__ vagina __x__ Zymbol gland __x__ All tissues with abnormalities

Not indicated as a required tissue in 1998 OPPTS Harmonized Test Guidelines

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246417

870.6200 Neurotoxicity Screening Battery - Acute -Rat

Does this study meet the following acceptance criteria?

No.	Yes/No	Crieter a
1	Y	Study c nducted under GLP (with statement).
2	Y	Technic l form of the active ingredient used.
3	N	Full ide tification of the test material (chemical identification, percentage active, l atch or lot number, physical properties, purity/impurities, expiration date, ve icle used, if any). It is preferable to use one lot throughout the study. **Purity/ Expiration Date: Not found.**
4	Y	Rat is n rmally used; under some circumstances mouse or dog may be more appropr ate, although not all of the battery may be adaptable to these species.
5	Y	Young 42+ days old) rats used.
6	Y	Oral do age (usual), with at leayst 3 doses, as well as vehicle control.
7	Y	Acute t st: max. dose 2 g/kg ory limit by toxicity. Subchronic: max. 1 g/kg or limit by toxicity.
8	N	Lowest dose produces minimal or no effects
9	Y	At leas 10M & 10F from each dose and vehicle control group used for behavic ral testing.
10	Y	At leas 5M & 5F/dose (and control group) used for terminal neuropathology (additic nal animals required if interim neuropathological examinations are conduc ed).
11	Y	For acu te studies, observations and activity testing made: __x__ Before dosing (or exposure). __x__ Estimated time of peak effect within 8 hrs of dosage (may be dose-specifi ; made by dosing pairs of rats across a range of doses and making regular observations of gait and arousal). __x__ At 7 and 14 days after dosing (or exposure).
12	Y	Observ ers in Functional Observational Battery (FOB) unaware of animal's treatm nt groups.

13	**(8) General level activity in open field and (15) fur appearance missing.**	**Functional Observational Battery criteria:** Assessment of signs of autonomic function, including: 1 Y Ranking (none to severe) of the degree of lacrimation & salivation. 2 Y Presence or absence of piloerection and exophthalmus. 3 Y Ranking or count of urination & defecation, including polyuria & diarrhea (usually in open field). 4 Y Pupillary function (constriction of pupil in response to light or measure of pupil size. 5 Y Degree of palpebral (eyelid) closure (e.g., ptosis or drooping of upper eyelid). Other effects, both in home cage and the open field, including: 6 Y Description, incidence and severity of any convulsions, tremors, or abnormal motor responses. 7 Y Ranking (range: no reaction to hyperreactivity) of subject's response to general stimuli such as removal from cage or handling. 8 N Ranking (range: unresponsive to hyperactive) of subject's general level of activity in open field. 9 Y Descriptions & incidence of posture and gait abnormalities in the home cage and open field. 10 Y Ranking (range: none to severe) of any gait abnormalities. 11 Y Forelimb and hindlimb grip strength measurements (preferably citing Meyer, 1979). 12 Y Quantitative measure of landing foot splay (preferably citing Edwards & Parker, 1977). 13 Y Responses to stimuli such as tail pinch, tail-flick or hot plate and/or to a sudden sound. 14 Y Individual body weights. 15 N Description & incidence of unusual or abnormal behavior, excessive or repetitive actions, emaciation, dehydration, hypotonia or hypertonia, altered fur appearance,deposits around eyes, nose or mouth. 16 Y Count of rearing activity on the open field. 17 Y Ranking of righting ability. 18 Y Individual body temperatures. _____ Alterations in rate and ease of respiration (presence of rales or dyspnea). _____ Sensorimotor responses to visual stimuli

14	**(3) Asymptotic levels by last 20% not found.**	**Motor Activity** 1 Y — Monitored by an automated recording apparatus capable of detecting increases & decreases in activity. 2 Y — Each animal tested individually. 3 N — Sessions with same duration, and long enough for motor activity to approach asymptotic levels by last 20% of session for untreated control animals.
15	**(5) None of the stains listed were used.**	**Neuropathology** 1 x — *In situ* perfusion used with an appropriate aldehyde fixative. 2 x — Tissues collected from central nervous system and from peripheral nervous system. 3 x — Central nervous system tissues embedded in paraffin or plastic. 4 x — Histological sections stained with hematoxylin and eosin or comparable stains. 5 ____ — Use of Bodian's or Bielchowsky's silver stain methods and/or glial fibrillary acidic protein. 6 x — Sections from high dose group first compared with those of the control group (if no alterations observed subsequent analysis of intermediate groups not required). NA — If evidence of alterations observed, sections from all dose groups from each region coded and examined in randomized orderby a person with knowledge of the code.
16	No	Positive control data from the laboratory conducting the testing, both for behavioral aspects and nervous system pathology.

ACCEPTANCE CRITERIA

Chemical: JAU6476 PC Code: 113961 MRID No.: 46246416

870.6200 Neurotoxicity Screening Battery - Subchronic - Rat

Does this study meet the following acceptance criteria?

No.	Yes/No	Crieteria
1	Y	Study conducted under GLP (with statement).
2	Y	Technical form of the active ingredient used.
3	N	Full identification of the test material (chemical identification, percentage active, batch or lot number, physical properties, purity/impurities, expiration date, vehicle used, if any). It is preferable to use one lot throughout the study. **Purity/Expiration Date: Not found.**
4	Y	Rat is normally used; under some circumstances mouse or dog may be more appropriate, although not all of the battery may be adaptable to these species.
5	Y	Young (42+ days old) rats used.
6	Y	Oral dosage (usual), with at least 3 doses, as well as vehicle control.
7	Y	Acute test: max. dose 2 g/kg or limit by toxicity. Subchronic: max. 1 g/kg or limit by toxicity.
8	Y	Lowest dose produces minimal or no effects
9	Y	At least 10M & 10F from each dose and vehicle control group used for behavioral testing.
10	Y	At least 5M & 5F/dose (and control group) used for terminal neuropathology (additional animals required if interim neuropathological examinations are conducted).
11	NA	For acute studies, observations and activity testing made: __X__ **FOB & Motor Activity weeks 4, 8 &13** __X__ Before dosing (or exposure). __No__ Estimated time of peak effect within 8 hrs of dosage (may be dose-specific; made by dosing pairs of rats across a range of doses and making regular observations of gait and arousal). __No__ At 7 and 14 days after dosing (or exposure).
12	Y	Observers in Functional Observational Battery (FOB) unaware of animal's treatment groups.

13	**(8) General level of activity in open field and (15) fur appearance missing.**	**Function al Observational Battery criteria:** Assessme nt of signs of autonomic function, including: 1 __Y__ F anking (none to severe) of the degree of lacrimation & salivation. 2 __Y__ F esence or absence of piloerection and exophthalmus. 3 __Y__ F anking or count of urination & defecation, including polyuria & diarrhea (usually in open field). 4 __Y__ F upillary function (constriction of pupil in response to light or measure of p pil size. 5 __Y__ I egree of palpebral (eyelid) closure (e.g., ptosis or drooping of upper e elid). Other eff ects, both in home cage and the open field, including: 6 __Y__ Description, incidence and severity of any convulsions, tremors, or a normal motor responses. 7__Y__ Ranking (range: no reaction to hyperreactivity) of subject's response to g neral stimuli such as removal from cage or handling. 8__N__ Ranking (range: unresponsive to hyperactive) of subject's general level of a tivity in open field. 9__Y__ Descriptions & incidence of posture and gait abnormalities in the home c ge and open field. 10__Y__ Ranking (range: none to severe) of any gait abnormalities. 11__Y__ Forelimb and hindlimb grip strength measurements (preferably citing M eyer, 1979). 12__Y__ Quantitative measure of landing foot splay (preferably citing Edwards & F arker, 1977). 13__Y__ Responses to stimuli such as tail pinch, tail-flick or hot plate and/or to a s dden sound. 14__Y__ Individual body weights. 15__Y__ Description & incidence of unusual or abnormal behavior, excessive or r petitive actions, emaciation, dehydration, hypotonia or hypertonia, a ltered fur appearance, deposits around eyes, nose or mouth. 16__Y__ Count of rearing activity on the open field. 17__Y__ Ranking of righting ability. 18__Y__ Individual body temperature.
14	**(3) Aerymptoti c levels by last 20% not found.**	**Motor a ctivity** 1 __Y__ Monitored by an automated recording apparatus capable of detectin g increases & decreases in activity. 2 __Y__ Each animal tested individually. 3 __N__ Sessions with same duration, and long enought for motor activity to approach asymptotic levels by last 20% of session for untreated control animals.

15	**(5) <u>None</u> of the stains listed were used.**	**<u>Neuropathology</u>** __Y__ *In situ* perfusion used with an appropriate aldehyde fixative. __Y__ Tissues collected from central nervous system and from peripheral nervous system. __Y__ Central nervous system tissues embedded in paraffin or plastic. __Y__ Histological sections stained with hematoxylin and eosin or comparable stains. __N__ Use of Bodian's or Bielchowsky's silver stain methods and/or glial fibrillary acidic protein. __Y__ Sections from high dose group first compared with those of the control group (if no alterations observed subsequent analysis of intermediate groups not required). __Y__ If evidence of alterations observed, sections from all dose groups from each region coded and examined in randomized orderby a person with knowledge of the code.
16	N	Positive control data from the laboratory conducting the testing, both for behavioral aspects and nervous system pathology.

ACCEPTANCE CRITERIA

Chemical: SXX0665 PC Code: 113961 MRID No.: 46246418

870.6[illegible]00 Developmental Neurotoxicity Study

Does this study meet the following acceptance criteria?

No.	Yes/No	Criteria
1	Y	Study co[illegible]ducted under GLP (with statement).
2	**Y**	Technica[illegible] form of the active ingredient used.
3	**Y**	Full iden[illegible]ification of the test material (chemical identification, percentage active, b[illegible]tch or lot number, physical properties, purity/impurities, expiration date, veh[illegible]cle used, if any). It is preferable to use one lot throughout the study.
4	**Y**	Preferre[illegible] species is rat; not the Fischer 344 strain. If the Fischer 344 rat strain or a mam[illegible]malian species other than the rat is used, justification must be provided[illegible].
5	**Y**	Identific[illegible]tion as to test animal strain and source.
6	Y	Young a[illegible]dult pregnant females (nulliparous) should be used.
7	Y	At least [illegible]0 litters/dose level, with at least 3 dose levels and a concurrent control group.
8	Y	If test su[illegible]bstance has been shown to be developmentally toxic, highest dose level should b[illegible]e maximum dose not inducing in utero or neonatal death or malform[illegible]ations that would preclude a meaningful evaluation of neurotoxicity. Otherwi[illegible]se, highest dose level should induce some overt maternal toxicity but should n[illegible]ot cause a reduction in weight gain exceeding 20 percent during gestatio[illegible] and lactation
9	Y	Lowest [illegible]dose should not produce any grossly observable evidence of either materna[illegible] or developmental toxicity
10	Y	Interme[illegible]diate dose(s) should be equally spaced between the highest and lowest [illegible]doses used. **40, 160, 500, ppm**
11	Y	Analyse[illegible]s for test material stability, homogeneity and concentration in dosing [illegible]medium. **Recommended, study may be acceptable if these criteria are met**

12	Y	Day 0 of gestation is the day on which a vaginal plug and/or sperm are observed. Dosing should be from day 6 of gestation through at least day 10 postnatally, but should not occur on the day of parturition in animals who have not completely delivered their offspring.
13	Y	Test material or vehicle administered orally; otherwise, justification provided.
14	Y	Gross examination of dams at least once each day before daily treatment (dosing)
15	Y	Ten dams per group observed outside home cage at least twice during gestationalperiod (days 6-21) and twice during lactational dosing period (days 1-10) for toxicity, with scoring (where appropriate) for the following: __Y__ Lacrimation __Y__ Pupillary function __Y__ Salivation __Y__ Palpebral closure (ptosis) __Y__ Piloerection __Y__ Convulsions, tremors, abnormal movements __Y__ Exophthalmus. __Y__ Posture and gait abnormalities __Y__ Urination (inc. polyuria) __Y__ Unusual behavior (inc. stereotypies) __Y__ Defecation (inc. diarrhea) __N__ Other symptoms (emaciation, dehydration, altered fur a appearance, red or crusty deposits around eyes, nose or mouth, etc.).
16	Y	Dams weighed at least weekly and on the day of delivery and postnatal days 11 and 21.
17	Y	Size of litters adjusted on postnatal day 4 to yield, as nearly as possible, 4 males and 4 females a litter, with partial adjustments (such as to 5 males and 3 females) when necessary. Elimination of runts only not appropriate.
18	Y	Individual pups identified uniquely after standardization of litter sizes.
19	Y	Testing not appropriate for litters with less than 7 pups
20	Y	After standardization of litter sizes, one male or one female per litter (total of 10 males and 10 females from each dosing group) should be randomly assigned for the following testing (some flexibility allowed; one group of 10M & 10F/dose level could be assigned to motor activity, another group consisting of 10M & 10Fdifferent animals to auditory startle, etc.): __X__ Motor activity __X__ Auditory startle __X__ Learning and memory

21	Y	On postn tal day 11, either one male or one female pup from each litter (total of 10 males and 10 females per dose group) should be sacrificed, and brain weights s ıould be measured for each. Of these pups, 6/sex/dose should be selected f or neuropathological examination. **PND.**
22	Y	At the te nination of the study, one male or one female pup from each litter (total of 0 males and 10 females per dose group) should be sacrificed, and brain we ghts should be measured for each. An <u>additional</u> group consisting of six anim ls per sex per dose group (no more than one animal per litter) should be sacrifi ced for neuropathological examination. **Additional group not was mention d.**
23	Y	Neuropa hological examinations should include the following: __Y__ S ıcrifice by CO_2 asphyxiation. __Y__ I rains removed, weighed, and fixed in an aldehyde fixative. __Y__ P astic embedding preferred, but paraffin is acceptable. __Y__ H istological sections stained with hematoxylin and eosin, or similar stains. __Y__ R epresentative sections examined by an appropriately trained patholog st __Y__ I sections from high dose group show no evidence of neuropathological alterations when compared with controls, no further analysis is required. __Y__ If evidence of neuropathological alterations found, then slides from i ıtermediate and low dose groups are examined. _____ *If neuropathological alterations are found, additional procedures (Bodian s or Bielchowsky's silver methods and/or immunochemistry for glial fibrillary acid protein) used..
24	Some areas not specifically mentioned.	Adequa e samples taken (and examined) from all brain regions, including: __Y__ Olfactory bulbs __Y__ Thalamus Midbrain, including: __Y__ Cerebral Cortex __Y__ Hypothalamus _____ Tectum __Y__ Hippocampus _____ Brainstem _____ Tegmentum _____ Basal ganglia __Y__ Cerebellum _____ Cerebral peduncles

25	**Not mentioned.**	Examination is for typical findings (such as neuronal vacuolation, degeneration, necrosis, astrocytic proliferation, leukocytic infiltration, cystic formation).
26	**Not mentioned.**	Examination is also for structural changes indicative of developmental insult including gross changes in size or shape of brain regions, death of neuronal precursors, abnormal proliferation or migration, alterations in transient development structures, abnormal differentiation, evidence of hydrocephalus).
27	Y	Some form of morphometric analysis performed on postnatal days 11 and at termination (at a minimum this would consist of an estimate of thickness of major layers at representative locations within neocortex, hippocampus, and cerebellum, possibly according to method of Rodier and Gramann). **PND.**
28	Y	Offspring observed at least daily for mortality or morbidity.
29	Y	A total of 10 male offspring and 10 female offspring/group should be examined by observers (who are unaware of their treatment group) outside the cage for thefollowing signs of toxicity (with scoring, when appropriate) on postnatal days 4,11, 21, 35, 45, and 60: __x__ Lacrimation _____ Pupillary function __x__ Salivation _____ Palpebral closure (ptosis) __x__ Piloerection __x__ Convulsions, tremors, abnormal movements __x__ Exophthalmus. __x__ Posture and gait abnormalities __x__ Urination (inc. polyuria) __x__ Unusual behavior (inc. stereotypies) __x__ Defecation (inc. diarrhea) __x__ Other symptoms (emaciation, dehydration, altered fur appearance, red or crusty deposits around eyes, nose or mouth, etc.).
30	**Y**	Developmental landmarks of offspring recorded: __x__ Pups weighed at or shortly after birth, and on postnatal days 4, 11, 17 and 21 and at least once every 2 weeks thereafter. __x__ Age of vaginal opening and preputial separation should be determined.
31	Y	Positive control data from the laboratory performing the test that demonstrate the sensitivity of the procedures being used. These data do not need to be from studies using prenatal exposures. However, the laboratory must demonstrate competence in evaluation of effects in neonatal animals perinatally exposed to chemicals and establish test norms for the appropriate age group. Historical control.

171-3 Directions For Use

SCREENING CRITERIA

The following criteria are provided as guidance to registrants concerning the directions for use that should appear on product labels for food use chemicals.
Each registrant must provide labels to EPA.

Do the Directions For Use meet the following criteria?

1. _y_ **Each formulation to be used identified with the concentration of active ingredient indicated (% by weight for solid formulations, pounds active ingredient per gallon for liquids)**

2. _y_ **All crops which are to be treated with each formulation clearly identified**

3. _y_ **Tolerance or exemption from tolerance proposed or established for each crop on proposed label**

4. _y_ **Impractical or unrealistic use restrictions excluded (e.g., restricting feed use of corn forage not practical due to high economic value and common practice of feeding to livestock)**

5. _y_ **Names and quantities of stickers spreaders, or other adjuvants to be added to spray solution**

6. _y_ **Field and orchard crop directions**
   - _y_ **Application rate in quantity of formulation and pounds active ingredient per acre (For row or band treatments indicate if the rate refers to the area treated or to the entire field)**
   - _y_ **Spray volumes to be used per acre**
   - _y_ **Maximum number applications per year of growing season**
   - _y_ **Minimum interval between successive applications**
   - _y_ **Minimum interval between last application and harvest (preharvest interval=PHI)**
   - na **For orchard crops additional information for full coverage sprays (quantity of formulation and pounds active ingredient per 100 gallons spray) and concentrated sprays (amount active per acre should be related to tree size)**

7. _y_ **Aerial, ultra low volume (ULV) and mist spray directions include spray concentration, amount of active ingredient per acre, and spray volume per acre**

8. na **Postharvest fumigation directions**
   - ___ **Dosage expressed in weight fumigant per volume of storage space or head space or weight fumigant per unit weight of commodity treated**
   - ___ **Temperature, pressure and duration of exposure specified**
   - ___ **Geometry and airtightness of containers described**
   - ___ **Aeration procedures and time of aeration specified**
   - ___ **Minimum interval between successive applications**

9. _na_ Animal treatment directions
   - ___ Concentration of pesticide i treatment solution
   - ___ Type of solvents, e.g. water oil, etc.
   - ___ Quantity of spray, pour-on olution, dust etc. to be applied per animal
   - ___ Amount of time animal to b held in dip tank
   - ___ Frequency of Treatment
   - ___ Maximum number of treat ents
   - ___ Preslaughter interval (inter al between last treatment and slaughter) specified (interval longer than 3 days usually not considered practical)

10. _na__ Aquatic use directions
   - ___ Dosage expressed in quanti y of formulation and pounds active ingredient per surface acre or parts per million pe ticide in the water (in latter case the amount product per surface area should be elated to average pond depth)
   - ___ Detailed description provid d for specialized equipment
   - ___ Minimum distance specifie from treated area to potable water or irrigation intake pipe
   - ___ If oxygen depletion proble s, proportion of pond to be treated and required interval between treatments
   - ___ Maximum number of appli ations per year
   - ___ Minimum interval between applications

11. _na__ Food handling establish nent use directions
   - ___ Type of establishment that nay be treated
   - ___ Dilution instructions and s ray concentration
   - ___ Type of application equipn ent and mode of application (space spray, directed spray to crevices, spot treatment etc.)
   - ___ Dosage limitations includin g cubic and square foot limitations
   - ___ Frequency of treatment
   - ___ Time of treatment (e.g., aft r-hours in restaurants)
   - ___ Instructions concerning re ioval and covering of food, dishes and utensils
   - ___ Cleanup procedures befor food processing, preparation or serving resumes

12. _na__ Agricultural premises treatn ents
   - ___ Description of areas to be t eated (e.g., feed lot, milking room, animal barn)
   - ___ Dosage specified (pounds p er unit volume treated for fogging applications; concentration of active ing edient in spray solutions; weight active ingredient per unit area of feed lot)
   - ___ Frequency of treatment
   - ___ Directions as to whether a imals should be removed during treatment

171-4(a) Nature of The Residue - Plants Study (wheat, peanuts & sugar beets)

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. **_y__ Pesticide radiolabeled in non-labile portion of molecule (tritium label strongly discouraged)**
2. **_y_ Separate studies conducted with radiolabel in each major functional group in pesticide molecule, e.g. benzene ring, pyrimidine ring, other cyclic/heterocyclic ring, etc.**
3. **_y_ Specific activity sufficient to permit detection of low residue levels (0.01-0.1 ppm range)**
4. **_y_ Radiochemically pure grade of active ingredient**
5. **_y__ Pesticide applied to plant in manner simulating expected use**
6. **_y__ Total radioactivity measured in plant parts used for human food or animal feed**
7. **_y__ Extractability of residue into solvents determined**
8. **_y__ Most of radioactivity extracted or exhaustive attempts (acid, base, enzyme) made to do so**
9. **_y__ Major components or portion of the terminal residue identified (preferably by at least two techniques-e.g., TLC, HPLC, MS)**

Note: The test compound was labeled on Phenyl-UL- ^{14}C and Triazole-UL-^{14}C.

171-4(b) Nature Of The Residue - Livestock----Poultry (Laying Hens)

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _y__ Pesticide radiolabeled in non-labile portion of molecule (tritium label strongly discouraged)

2. _y_ Separate studies conducted with radiolabel in each major functional group in pesticide molecule, e.g. benzene ring, pyrimidine ring, other cyclic/heterocyclic ring, etc.

3. _y_ Specific activity sufficient to permit detection of low residue levels (0.01-0.1 ppm range)

4. _y__ Radiochemically pure grade of active ingredients used for dosing

5. _y__ Pesticide administered orally to animals for at least three consecutive days (or applies externally for at least 3 consecutive days using a method of application specified in label directions)

6. _y__ Ruminant and poultry studies provided, if crop commodities can be fed to both ruminants and poultry

7. _y__ Animals not preconditioned by dosing with unlabeled material

8. _y__ Animals sacrificed within 24 hours of final dose or application

9. _y__ Total radioactivity measured in edible tissues (muscle, fat, liver, ruminant kidney) and milk or eggs

10. _y_ Extractability of residue into solvents determined

11. _y_ Most radioactivity extracted or exhaustive attempts (acid, base, enzyme) made to do so

12. _y_ Major components or portion of the terminal residue identified (preferably by at least two techniques-e.g., TLC, HPLC, MS) in edible tissues and milk or eggs

Note: The test compound was labeled on Phenyl-UL- ^{14}C and Triazole-UL-^{14}C.

171-4(b) Nature Of The Residue - Livestock—Lactating Goat

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _y__ **Pesticide radiolabeled in non-labile portion of molecule (tritium label strongly discouraged)**

2. _y__ **Separate studies conducted with radiolabel in each major functional group in pesticide molecule, e.g. benzene ring, pyrimidine ring, other cyclic/heterocyclic ring, etc.**

3. _y_ **Specific activity sufficient to permit detection of low residue levels (0.01-0.1 ppm range)**

4. _y__ **Radiochemically pure grade of active ingredients used for dosing**

5. _y__ **Pesticide administered orally to animals for at least three consecutive days (or applies externally for at least 3 consecutive days using a method of application specified in label directions)**

6. _y__ **Ruminant and poultry studies provided, if crop commodities can be fed to both ruminants and poultry**

7. _y__ **Animals not preconditioned by dosing with unlabeled material**

8. _y__ **Animals sacrificed within 24 hours of final dose or application**

9. _y__ **Total radioactivity measured in edible tissues (muscle, fat, liver, ruminant kidney) and milk or eggs**

10. _y_ **Extractability of residue into solvents determined**

11. _y_ **Most radioactivity extracted or exhaustive attempts (acid, base, enzyme) made to do so**

12. _y_ **Major components or portion of the terminal residue identified (preferably by at least two techniques-e.g., TLC, HPLC, MS) in edible tissues and milk or eggs**

Note: The test compound was labeled on Phenyl-UL- ^{14}C and Triazole-UL-^{14}C.

171-4(c) & (d) Residue Analytical Method -Plant (Method RPA JA/03/01)

SCREENING CRITERIA

1. _y__ List of equipment, reagents and standards provided along with U.S. sources/suppliers of same
2. _y__ Instrumentation and operating conditions described
3. _y__ Detailed description of each step in procedure to enable use by competent analyst unfamiliar with method
4. _y__ Discrete response for analyte
5. _y__ Control values reasonably low compared to tolerance
6. _y__ Adequate recoveries (generally 70%) obtained for fortifications at the tolerance level
7. _y__ Recoveries don't vary significantly from sample to sample
8. _y__ Evidence that weathered and aged residues extracted by procedure (may reference work in metabolism studies)
9. _y__ Data showing that method releases and recovers bound residues (if latter of toxicological concern)
10. _y__Provides an enforcement method which:
    - _y__ Does not require untreated commodity as blank
    - _y__ Does not require internal or procedural standard to correct for recoveries (Addition of internal standard in final step just prior to injection is acceptable for calibration of retention times. However, use of internal standard throughout entire procedure to correct for recoveries is not acceptable unless data are available on numerous samples of each matrix to show analyte and internal standard behave identically in each step.)
    - _y__ Does not require exotic equipment or reagents
    - _y__ Reasonably rapid in execution
    - _y__ Specific to measure residue in presence of other reasonably expected pesticides
    - ___ Identifies level of detection (LOD) and level of quantification (LOQ)
    - _y__ Sensitive in relation to tolerance
    - _y__ Confirmatory method available
    - _y__ Method not claimed to be Confidential Business Information
    - _y__ Does not use hazardous reagents (justification needed for use of benzene as solvent or *diazomethane as methylating agent*)
11. _y__ If a new chemical or new proposed enforcement method, Second Laboratory Validation Study is submitted

171-4(c) & (d) Residue Analytical Method—Animal Commodities

SCREENING CRITERIA

1. _y__ List of equipment, reagents and standards provided along with U.S. sources/suppliers of same

2. _y__ Instrumentation and operating conditions described

3. _y__ Detailed description of each step in procedure to enable use by competent analyst unfamiliar with method

4. _y__ Discrete response for analyte

5. _y__ Control values reasonably low compared to tolerance

6. _y__ Adequate recoveries (generally ≥70%) obtained for fortifications at the tolerance level

7. _y__ Recoveries don't vary significantly from sample to sample

8. _y__ Evidence that weathered and aged residues extracted by procedure (may reference work in metabolism studies)

9. _y__ Data showing that method releases and recovers bound residues (if latter of toxicological concern)

10. _y__Provides an enforcement method which:
    - _y__ Does not require untreated commodity as blank
    - _y__ Does not require internal or procedural standard to correct for recoveries (Addition of internal standard in final step just prior to injection is acceptable for calibration of retention times. However, use of internal standard throughout entire procedure to correct for recoveries is not acceptable unless data are available on numerous samples of each matrix to show analyte and internal standard behave identically in each step.)
    - _y__ Does not require exotic equipment or reagents
    - _y__ Reasonably rapid in execution
    - _y__ Specific to measure residue in presence of other reasonably expected pesticides
    - ___ Identifies level of detection (LOD) and level of quantification (LOQ)
    - _y__ Sensitive in relation to tolerance
    - _y__ Confirmatory method available
    - _y__ Method not claimed to be Confidential Business Information
    - _y__ Does not use hazardous reagents (justification needed for use of benzene as solvent or diazomethane as methylating agent)

11. _y__ If a new chemical or new proposed enforcement method, Second Laboratory Validation Study is submitted

171-4(e) Storage Stability

SCREENING CRITERIA

Does the study meet the following accepta nce criteria?

1. _y__ Sample preparation and fortifica ion described (or in cases where samples with weathered residues are used, history of crop and pesticide treatment provided)

2. _y__ Storage conditions specified (tem perature, containers, form of r.a.c., lighting, etc.)

3. _y__ Dates of fortification (or harvest in case of field treated samples), placement into storage, sampling, and residue analysis p ovided

4. _y__ All components of total toxic res due fortified into commodity (or present from field treatment with pesticide) and measured by validated analytical method(s) (description of latter provided or referenced)

5. _y__ Storage conditions are (e.g. stora ge containers, physical state, temperature, time period) the same for both fortified samples a nd field residue samples

Storage intervals:

Wheat (forage, grain, straw, flour and b an) from 189 -198 days
Mustard green 196 days
Turnip roots 196 days
Tomato fruit 193 days
paste 230 days
Canola seed 190 days
oil 231 days
meal 190 days

Note: Field trial samples of rice, b arley, peanuts, canola, and wheat were maintained in frozen storage for a maximum of 1197 to 1261 days before analysis. The available storage stability data are only 190 to 230 days. The petition er states that the storage stability studies are in process.

171-4(j) Meat, Milk, Poultry, Egg-Feeding—Dairy Cattle & Poultry

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. **_y__ Compound(s) fed corresponds to residues expected on feed items**

2. **_y__ Several dosages examined with one approximating intake expected from treated feed items, one or more representing exaggerated intake, and one control group**

3. **_y__ Multiple animals included in each dosage group (preferably at least 3 for cattle and 10 for poultry)**

4. **_y__ Duration of dosing adequate to ensure residues plateau in milk and eggs (preferably at least 4 weeks**

5. **_y__ Animals sacrificed within 24 hours of final dose**

6. **_y__ Total toxic residue measured in edible tissues (muscle, fat, liver, kidney), milk, and eggs of both control and treated animals using validated analytical method (description of latter given or referenced)**

7. **___ Analytical method sufficiently sensitive (0.01-0.05 ppm)**

8. **_y__ Description of handling and dosing of animals, feed consumption, and sample collection, handling and storage provided**

9. **__y_ Storage stability dada available reflecting storage of tissue, milk and egg samples prior to residue analysis (may be referenced to separate study)**

Note: Poultry feeding study not necessary if all crop commodities feed to non-poultry only

171-4(k) Magnitude of the Residue-Crop Field Trails—Barley

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _n_ Crop treated according to label directions leading to *maximum residues:*
   - _y_ Maximum application rate and number of applications
   - _y_ Minimum retreatment intervals
   - _n_ Minimum preharvest interval
   - _y_ Minimum spray volume

2. _y_ Data reflects modes of application on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/sticker

3. _y_ Formulation proposed for registration used in residue field studies

4. _y_ Trial locations represent all principal growing regions (adequate "geographic representation") OR minor crop for which regional registration is accepted

5. _y_ Sufficient number of trials conducted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importance of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use-e.g., early season/pre-emergence versus late season foliar)

6. _y_ Residue decline studies included if residues present at or close to harvest for crops with >5 field trials

7. _y_ Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for food or feed (except for *feed items which are restricted by product* labels)

8. _y_ Description of sample treatment collection, handling (including any washing or trimming) and storage provided (covering periods from planting to harvest and from harvest through analysis)

9. _y_ Dates of treatment, harvest, entry into storage, and residue analysis

10. _n_ Storage stability data available reflecting storage of crop samples (may be referenced to separate study)

171-4(k) Magnitude of the Residue-Crop Field Trails— Canola

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _n_ **Crop treated according to label directions leading to maximum residues:**
   - _y_ **Maximum application rate and number of applications**
   - _n_ **Minimum retreatment intervals**
   - _y_ **Minimum preharvest interval**
   - _y_ **Minimum spray volume**

2. _y_ **Data reflects modes of application on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/stickers**

3. _y_ **Formulation proposed for registration used in residue field studies**

4. _y_ **Trial locations represent all principal growing regions (adequate "geographic representation") OR minor crop for which regional registration is accepted**

5. _y_ **Sufficient number of trials conducted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importance of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use-e.g., early season/pre-emergence versus late season foliar)**

6. _y_ **Residue decline studies included, if residues present at or close to harvest for crops with >5 fieldtrials**

7. _y_ **Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for food or feed (except for feed items which are restricted by product labels)**

8. _y_ **Description of sample treatment, collection, handling (including any washing or trimming) and storage provided (covering periods from planting to harvest and from harvest through analysis)**

9. _y **Dates of treatment, harvest, entry into storage, and residue analysis**

10. _n_ **Storage stability data available reflecting storage of crop samples (may be referenced to separate study)**

171-4(k) Magnitude o : the Residue-Crop Field Trails—Dried Peas & Beans (crop subgroup 6c)

SCREENING CRITERIA

Does the study meet the following accepta ıce criteria?

1. _y_ Crop treated according to label c irections leading to maximum residues:
   - _y_ Maximum application rate nd number of applications
   - _y_ Minimum retreatment inte vals
   - _y_ Minimum preharvest inter al
   - _y_ Minimum spray volume

2. _y_ Data reflects modes of applicatio ı on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/sticker

3. _y_ Formulation proposed for regist ation used in residue field studies

4. _y_ Trial locations represent all prin ipal growing regions (adequate "geographic representation") OR minor crop for which region ıl registration is accepted

5. _y_ Sufficient number of trials condı cted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importan e of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use-e .g., early season/pre-emergence versus late season foliar)

6. _y_ Residue decline studies included if residues present at or close to harvest for crops with >5 field trials

7. _y_ Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for food or feed (except for feed items which are restricted by product labels)

8. _y_ Description of sample treatment collection, handling (including any washing or trimming) and storage provided (covering perio ds from planting to harvest and from harvest through analysis)

9. _y_ Dates of treatment, harvest, ent y into storage, and residue analysis

10. _n_ Storage stability data available eflecting storage of crop samples (may be referenced to separate study)

171-4(k) Magnitude of the Residue-Crop Field Trails—Peanuts

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _y_ **Crop treated according to label directions leading to maximum residues:**
   - _y_ **Maximum application rate and number of applications**
   - _y_ **Minimum retreatment intervals**
   - _y_ **Minimum preharvest interval**
   - _y_ **Minimum spray volume**

2. _y_ **Data reflects modes of application on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/stickers**

3. _y_ **Formulation proposed for registration used in residue field studies**

4. _y_ **Trial locations represent all principal growing regions (adequate "geographic representation") OR minor crop for which regional registration is accepted**

5. _y_ **Sufficient number of trials conducted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importance of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use-e.g., early season/pre-emergence versus late season foliar)**

6. _y_ **Residue decline studies included, if residues present at or close to harvest for crops with >5 field trials**

7. _y_ **Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for food or feed (except for feed items which are restricted by product labels)**

8. _y_ **Description of sample treatment, collection, handling (including any washing or trimming) and storage provided (covering periods from planting to harvest and from harvest through analysis)**

9. _y_ **Dates of treatment, harvest, entry into storage, and residue analysis**

10. _n_ **Storage stability data available reflecting storage of crop samples (may be referenced to separate study)**

171-4(k) Mag itude of the Residue-Crop Field Trails----Rice

SCREENING CRITERIA

Does the study meet the following accept: nce criteria?

1. _n_ **Crop treated according to label c irections leading to maximum residues:**
   - y **Maximum application rate an l number of applications**
   - n **Minimum retreatment interv: ls**
   - n **Minimum preharvest interva**
   - y ***Minimum spray volume***

2. _y_ **Data reflects modes of applicatio n on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/sticker**

3. _y_ **Formulation proposed for regis: ration used in residue field studies**

4. _y_ **Trial locations represent all prin :ipal growing regions (adequate "geographic representation") OR minor crop for which region il registration is accepted**

5. _y_ **Sufficient number of trials cond: cted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importan: e of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use-: .g., early season/pre-emergence versus late season foliar)**

6. _y_ **Residue decline studies includec , if residues present at or close to harvest for crops with >5 field trials**

7. _y_ **Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for foo: or feed (except for feed items which are restricted by product labels)**

8. _y_ **Description of sample treatmen collection, handling (including any washing or trimming) and storage provided (covering peri: ds from planting to harvest and from harvest through analysis)**

9. _y_ **Dates of treatment, harvest, ent y into storage, and residue analysis**

10. _n_ **Storage stability data available eflecting storage of crop samples (may be referenced to separate study)**

171-4(k) Magnitude of the Residue-Crop Field Trails—Wheat

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _y_ **Crop treated according to label directions leading to maximum residues:**
   - _y_ **Maximum application rate and number of applications**
   - _y_ **Minimum retreatment intervals**
   - _y_ **Minimum preharvest interval**
   - _y_ **Minimum spray volume**

2. _y_ **Data reflects modes of application on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/stickers**

3. _y_ **Formulation proposed for registration used in residue field studies**

4. _y_ **Trial locations represent all principal growing regions (adequate "geographic representation") OR minor crop for which regional registration is accepted**

5. _y_ **Sufficient number of trials conducted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importance of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use-e.g., early season/pre-emergence versus late season foliar)**

6. _y_ **Residue decline studies included, if residues present at or close to harvest for crops with >5 field trials**

7. _y_ **Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for food or feed (except for feed items which are restricted by product labels)**

8. _y_ **Description of sample treatment, collection, handling (including any washing or trimming) and storage provided (covering periods from planting to harvest and from harvest through analysis)**

9. _y_ **Dates of treatment, harvest, entry into storage, and residue analysis**

10. _n_ **Storage stability data available reflecting storage of crop samples (may be referenced to separate study)**

171-4(k) Magnitude of the Residue Crop Field Trails----Field Rotation Crops (wheat, mustard greens and turnips)

SCREENING CRITERIA

Does the study meet the following accept: nce criteria?

1. _y_ Crop treated according to label directions leading to maximum residues:
   Maximum application rate and number of applications
   _Minimum retreatment interval
   _Minimum preharvest interval
   Minimum spray volume

2. _NA Data reflects modes of applicati n on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/sticker

3. _y_ Formulation proposed for regis ration used in residue field studies

4. _NA Trial locations represent all pri cipal growing regions (adequate "geographic representation") OR minor crop for which regio l registration is accepted

5. _y_ Sufficient number of trials cond cted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importan e of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use- .g., early season/pre-emergence versus late season foliar)

6. _NA Residue decline studies includ l, if residues present at or close to harvest for crops with >5 field trials

7. _y_ Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for foo or feed (except for feed items which are restricted by product labels)

8. _y_ Description of sample treatmen collection, handling (including any washing or trimming) and storage provided (covering peri ds from planting to harvest and from harvest through analysis)

9. _y_ Dates of treatment, harvest, ent y into storage, and residue analysis

10. _n_ Storage stability data available eflecting storage of crop samples (may be referenced to separate study)

171-4(k) Magnitude of the Residue---- Rotation Crops (wheat, Swiss chard and turnips)

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _y_ Crop treated according to label directions leading to maximum residues:
   Maximum application rate and number of applications
   _Minimum retreatment intervals
   _Minimum preharvest interval
   Minimum spray volume

2. _NA Data reflects modes of application on label: ground, aerial, oil diluents, use of adjuvants such as surfactants and spreader/stickers

3. _y_ Formulation proposed for registration used in residue field studies

4. _NA Trial locations represent all principal growing regions (adequate "geographic representation") OR minor crop for which regional registration is accepted

5. _y_ Sufficient number of trials conducted to determine an appropriate tolerance or maximum residue level (factors to consider include seasonal and yearly variations, differences in varieties and cultural practices, the importance of the crop, the toxicity of the pesticide and its ability to translocate, and the type of use-e.g., early season/pre-emergence versus late season foliar)

6. NA Residue decline studies included, if residues present at or close to harvest for crops with >5 field trials

7. _y_ Total toxic residue measured by validated analytical method (description provided or referenced) on all parts of crop used for food or feed (except for feed items which are restricted by product labels)

8. _y_ Description of sample treatment, collection, handling (including any washing or trimming) and storage provided (covering periods from planting to harvest and from harvest through analysis)

9. _y_ Dates of treatment, harvest, entry into storage, and residue analysis

10. _y_ Storage stability data available reflecting storage of crop samples (may be referenced to separate study)

17 -4(l) Processed Food/Feed—Barley

SCREENING CRITERIA

Does the study meet the following accept: nce criteria?

1. __ The raw agricultural commodity (r.a.c.) samples that were processed contained field-treated detectable residues (preferably a or above the tolerance) OR r.a.c. was treated in the field at exaggerated rates in an attempt o get detectable residues .

2. __ *The r.a.c. was processed using p ·ocedures simulating commercial practices*

3. __ The total toxic residue was meas ıred with a validated analytical method (description provided or MRID # referenced) in the r.a.c. and all its byproducts listed in Table 2 of the Residue Chemistry Guidelines

4. __ Description of pesticidal treatme ıt and processing of r.a.c. and collection, handling and storage of samples provided

5. __ Storage stability data available ı eflecting storage of r.a.c. and byproduct samples (may be referenced to separate study)

Note: The petitioner did not subm it a processing study for barley. Based on OPPTS 860.1520, wheat processing study can be translatec to barley.

171-4(l) Processed Food/Feed—Canola

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _y_ **The raw agricultural commodity (r.a.c.) samples that were processed contained field-treated detectable residues (preferably at or above the tolerance) OR r.a.c. was treated in the field at exaggerated rates in an attempt to get detectable residues .**

2. _y_ **The r.a.c. was processed using procedures simulating commercial practices**

3. _y_ **The total toxic residue was measured with a validated analytical method (description provided or MRID # referenced) in the r.a.c. and all its byproducts listed in Table 2 of the Residue Chemistry Guidelines**

4. _y_ **Description of pesticidal treatment and processing of r.a.c. and collection, handling and storage of samples provided**

5. _n_ **Storage stability data available reflecting storage of r.a.c. and byproduct samples (may be referenced to separate study)**

171 4(l) Processed Food/Feed—Peanuts

SCREENING CRITERIA

Does the study meet the following accepta nce criteria?

1. _y_ The raw agricultural commodity (r.a.c.) samples that were processed contained field-treated detectable residues (preferably a or above the tolerance) OR r.a.c. was treated in the field at exaggerated rates in an attempt t o get detectable residues .

2. _y_ The r.a.c. *was processed using p ocedures simulating commercial practices*

3. _y_ The total toxic residue was meas red with a validated analytical method (description provided or MRID # referenced) in the r.a.c. and all its byproducts listed in Table 2 of the Residue Chemistry Guidelines

4. _y_ Description of pesticidal treatme it and processing of r.a.c. and collection, handling and storage of samples provided

5. _n_ Storage stability data available r eflecting storage of r.a.c. and byproduct samples (may be referenced to separate study)

171-4(l) Processed Food/Feed—Rice

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. _y_ **The raw agricultural commodity (r.a.c.) samples that were processed contained field-treated detectable residues (preferably at or above the tolerance) OR r.a.c. was treated in the field at exaggerated rates in an attempt to get detectable residues .**

2. _y_ **The r.a.c. was processed using procedures simulating commercial practices**

3. _y_ **The total toxic residue was measured with a validated analytical method (description provided or MRID # referenced) in the r.a.c. and all its byproducts listed in Table 2 of the Residue Chemistry Guidelines**

4. _y_ **Description of pesticidal treatment and processing of r.a.c. and collection, handling and storage of samples provided**

5. _n_ **Storage stability data available reflecting storage of r.a.c. and byproduct samples (may be referenced to separate study)**

171-4(l) Processed Food/Feed—W eat (grain, aspirated grain fraction, bran, flour, germ, middl ngs and shorts)

SCREENING CRITERIA

Does the study meet the following accepta ace criteria?

1. _y_ **The raw agricultural commodity (r.a.c.) samples that were processed contained field-treated detectable residues (preferably a or above the tolerance) OR r.a.c. was treated in the field at exaggerated rates in an attempt t) get detectable residues .**

2. _y_ **The r.a.c. was processed using p ocedures simulating commercial practices**

3. _y_ **The total toxic residue was meas red with a validated analytical method (description provided or MRID # referenced) in the r.a.c. and all its byproducts listed in Table 2 of the Residue Chemistry Guidelines**

4. _y_ **Description of pesticidal treatme it and processing of r.a.c. and collection, handling and storage of samples provided**

5. _n_ **Storage stability data available r eflecting storage of r.a.c. and byproduct samples (may be referenced to separate study)**

171-6 Proposed Tolerance

SCREENING CRITERIA

Does the study meet the following acceptance criteria?

1. **_y__ Tolerance expression includes complete, accepted chemical names of parent pesticide and metabolites of toxicological concern**

2. **_y__ Tolerance includes proper name or description of commodity or crop group**

3. **_n__ Tolerance high enough to cover any residue values reasonably expected based on residue data (i.e., tolerance not based on average residues, but on maximum residue)**

4. **_n_ Tolerance not set higher than necessary.**

5. **_na_ Specification of conditions of use of pesticide for food additive regulations covering use in food handling establishments**

13544

R103108

Chemical:	**Prothioconazole**
PC Code:	**113961**
HED File Code	***13000 Tox Reviews***
Memo Date:	**10/04/2004**
File ID:	**DPD309007**
Accession Number:	**412-05-5000**

HED Records Reference Center
10/26/2004