12-10-90

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ALLETHRIN

Chemical Code # 000012, Tolerance # 113
SB 950 # 247

November 16, 1987
Revised 11/10/88, 12/10/90

I. DATA GAP STATUS

Chronic toxicity, rat:	no data gap, no adverse effect
Chronic toxicity, dog:	no data gap, no adverse effect
Oncogenicity, rat:	no data gap, no adverse effect
Oncogenicity, mouse:	no data gap, no adverse effect
Reproduction, rat:	no data gap, no adverse effect
Teratogenicity, rat:	no data gap, no adverse effect
Teratogenicity, rabbit:	no data gap, no adverse effect
Gene mutation:	no data gap, no adverse effect
Chromosome effects:	no data gap, no adverse effect
DNA damage:	no data gap, no adverse effect
Neurotoxicity:	not required at this time

Note, Toxicology one-liners are attached

All volume numbers through 136 and record numbers through 085132 & 933397 were examined.
** indicates acceptable study
Bold face indicates possible adverse effect
File name : T901210
Revised by H. Green and Stanton Morris, 11/20/89; M. Silva, 12/10/90

NOTE: EPA guidelines for reregistration of allethrin was published on March 24, 1988.

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II. TOXICOLOGY SUMMARY

EPA has found that esbiothrin may be used as a representative test material for chronic studies on bioallethrin (d-trans allethrin) and S-bioallethrin but separate chronic toxicity studies are required for allethrin (pynamin) and d-cis, trans allethrin (d-allethrin, pynamin-forte; "Guidance for the Reregistration of Pesticide Products Containing Allethrin Stereoisomers as the Active Ingredient", EPA, 1988, p. 20). Only studies conducted with d-cis, trans allethrin (d-allethrin, pynamin-forte) were evaluated by CDFA (Morris, 11/20/89).

COMBINED, RAT

** 107; 052543; "Chronic Toxicity and Oncogenicity Study of Pynamin Forte in Rats"; Daiyu-Kai Institute of Medical Science; 5/15/85; Allethrin (91-91% purity; lot # 91007 & 10111) was administered to F344/DuCrj rats at dietary doses of 0 (vehicle = corn oil), 125, 500 and 2000 ppm for 123 weeks and a satellite study for 78 weeks. Adequacy of dose demonstrated by decreased body weight gain at 2000 ppm (NOEL = 500 ppm). No other significant toxicology findings were reported. No adverse effect was indicated. All deficiencies in the original review (Luthra, 11/02/87) were adequately addressed: brain and spinal cord serial sections not evaluated, test material stability in feed not established, no pilot study, no protocol, no QA statement, no analysis of test material, randomization procedure not stated, statistical analysis inappropriate, results not fully described (Silva, 10/26/88), and no eye exam (Morris, 11/21/89). The study is acceptable.

123; 075050; "Chronic Toxicity of Pynamin Forte in Dogs", HLA Study No. 343-207": Evaluation of ophthalmology data in this study resulted in a waiver for additional submissions of eye data and finding acceptable the study at doc. # 113-107, rec. # 052543

116 070526 "Stability of Pynamin Forte in the Rodent Diet," (Sumitomo Chemical Company, Ltd., 8/11/88). This volume contains an analysis of allethrin in rodent diet for study 107 052543. No worksheet was made for this information. M. Silva, 10/25/88.

116 070527 "Protocol for Combined Chronic Toxicity/Oncogenicity Studies," (Daiyu-Kai Institute of Medical Science, 7/18/88). This volume contains a protocol for the rat combined (chronic/oncogenicity) study 107 052543. No worksheet was made for this information. M. Silva, 10/25/88.

116 070528 "Dose-Finding Study (Preliminary Study) of Pynamin Forte in Rats," (Daiyu-Kai Institute of Medical Science, in-life portion 1980, translated from Japanese 7/18/88). Pynamin Forte (allethrin technical, Lot No. 91007, purity = 91.9%) was fed to F344/DuCrj rats at 0 (vehicle = corn oil), 625, 1250, 2500, 5000 and 10,000 ppm for 5 weeks (10/sex/group). **No adverse effect indicated.** NOEL = 625 ppm (decreased body weight gain in both sexes at 10,000 ppm; in males at ≥ 1250 ppm and females at ≥ 5000 ppm; the specific gravity of urine was significantly increased; in males at 10,000 ppm, erythrocyte count, hemoglobin concentration and hematocrit values were significantly decreased; at ≥ 625 ppm significant decreases in serum triglyceride were observed in both sexes -- this was the only "effect" observed at 625 ppm; in males at ≥ 2500 ppm and in females at ≥ 5000 ppm significant increases in serum total protein were observed; liver weights in males were significantly increased at ≥ 1250 ppm and in females at ≥ 5000 ppm; kidney weights in

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males were significantly increased at 10,000 ppm; hepatocytomegaly was observed in the liver of both sexes at 10,000 ppm). **Not acceptable** (no ophthalmological exam; inadequate histopathology). **Not upgradeable. This study is a pilot for 107 052543.** M. Silva, 10/25/88.

113 067673 "Amendment of the report: Chronic Toxicity and Oncogenicity Study of Pynamin Forte in Rats," (Daiyu-Kai Institute of Medical Science, 4/22/88). This volume contains a revision of the QA statement for study 107 052543, in order to add the date of inspection or review into the report. M. Silva, 10/26/88.

CHRONIC TOXICITY, DOG

** 123; 075050; "Chronic Toxicity of Pynamin Forte in Dogs", HLA Study No. 343-207"; Hazleton Laboratories America, Inc., Vienna, VA; 03/14/89; pynamin forte, lot # 70202, 93.4% stated purity; Groups of 6 dogs/sex were dosed orally by capsule with 0, 6, 20, 60, or 100 (200 for first week) mg/kg/day for 52 weeks. Dose-related symptoms, characteristic of acute pyrethroid toxicity, were seen at 20, 60, and 100 (200) mg/kg/kg including lethal seizures at 100 (3/sex) and 200 (1/sex) mg/kg/day (NOEL = 6 mg/kg/day). Dose-related increases in relative liver weights were seen through 60 mg/kg/day. No adverse effect was demonstrated. The study is acceptable (Morris, 11/20/89).

ONCOGENICITY, MOUSE

** 129 075943, "Pynamin Forte Potential Tumorigenic Effects in Prolonged Dietary Administration in Mice (KT-91-0086)", (Mayfield, R., Gopinathy, C., et al., Huntingdon Research Centre Ltd., England, report # SMO 247/881028, 3/20/89). Pynamin Forte (93.1% pure, lot #: 50310) was fed in the diet for 81 weeks at 0 (Labsure Laboratory Animal Diet No. 2 (LAD 2)), 120, 600, and 3000 ppm with 88 Charles River CD-1 mice/sex/group (36/sex/group were designated satellite groups for blood sampling and sacrifice at 52 and 78 weeks). **No adverse effect indicated.** Chronic NOEL = 600 ppm (Increased absolute and relative group mean liver weights were observed in both sexes at 3000 ppm at 52, 78, and 82 weeks. Increased centrilobular hepatocyte enlargement, centrilobular hepatocyte vacuolation and centrilobular fat deposition was observed in 3000 ppm males at terminal sacrifice.) Oncogenicity NOEL $\geq$ 3000 ppm. **Acceptable.** (H. Green & M. Silva, 9/25/90).)

REPRODUCTION, RAT

**128 075942, "Reproductive Effects of Pynamin Forte Administered Orally in Feed to Crl:COBS•CD•(SD)BR Rats for Two Generations", (Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA., report # 1119-002, 3/29/89), Pynamin Forte (allethrin, 93.4% pure, lot #: 70202) was fed in the diet through 2 generations, 1 litter/generation (treatment began 83 days prior to mating in both generations) at 0, 200, 2000, and 6000 ppm to $\geq$ 30 Crl:COBS•CD•(SD)BR rats/sex/group. Chronic NOEL = 200 ppm (There was

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decreased food consumption in both sexes of F0 and F1 during the premating period at 6000 ppm. Bodyweights were reduced in both sexes of F0 and F1 during the periods tested at 6000 ppm. Both F0 and F1 showed significantly increased liver weights at ≥ 2000 ppm. Hepatocellular hypertrophy was observed in females at 6000 ppm and in males at ≥ 2000 ppm.) Reproductive NOEL = 2000 ppm (Pup bodyweights were significantly reduced in the F0 offspring at ≥ 4 days). **No adverse effect. Acceptable.** (H. Green & M. Silva, 9/19/90)

TERATOLOGY, RAT

Sub acute and rangefinding studies:

133 085127, "Pynamin - Forte: Ten Day Oral Toxicity Study in Female Rats (KT-91-0092)", (Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA., project # 1119-003, 7/17/89). Pynamin Forte (93.4% pure, lot #50310) was administered daily by gavage at 0 (0.5% methylcellulose), 50, 100, 200, 300, 400, and 800 mg/kg/day to virgin female Crl:COBS•CD•(SD)BR rats (5/group). NOEL = 200 mg/kg/day (1/5, 1/5, and 4/5 deaths occurred at 300, 400, and 800 mg/kg/day respectively. Tremors were reported in 3/5, 3/5, and 3/5 at 300, 400, and 800 mg/kg/day respectively.) **Supplemental** information (Preliminary to range-finding teratology study in rats, project 1119-004P, record # 085128). (H. Green, & M. Silva, 9/12/90).

133 085128, "Range-Finding Teratology Study in Rats (KT-91-0093)", (Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA., project # 1119-004P, 7/17/89). Pynamin Forte (93.4% pure; lot #: 50310) was administered by gavage to mated Crl:COBS•CD•(SD)BR (8/group) on days 6 through 15 of gestation (day 0 of gestation = presence of a sperm plug) at 0 (0.05% w/v methylcellulose), 50, 100, 200 and 300 mg/kg/day. **No adverse effect indicated.** Maternal NOEL = 50 mg/kg/day (Tremors occurred approximately 30 to 60 minutes after dosing at ≥ 100 mg/kg/day.) Developmental NOEL ≥ 300 mg/kg/day (No external alteration was reported in any fetus on study.) **Supplemental** to record # 085129. (H. Green & M. Silva, 9/6/90)

Teratology, rat:

** 134 085129, "Teratology Study in Rats with Pynamin Forte (KT-91-0094)", (Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA., Project # 1119-004, 7/17/89). Pynamin Forte (allethrin, 93.4% pure; lot #: 50310) was administered by gavage to mated Crl:CD•(SD)BR female rats (25/group) on days 6 through 15 of gestation (day 0 = detection of sperm plug) at 0 (0.5% w/w methylcellulose), 10, 30, and 100 mg/kg/day. **No adverse effect.** Maternal NOEL = 30 mg/kg/day (Maternal tremors and excess salivation were observed at 100 mg/kg/day). Developmental NOEL ≥ 100 mg/kg/day (No remarkable fetal gross external, soft tissue or skeletal effects were reported.) **Acceptable.** (H. Green & M. Silva, 9/6/90).

TERATOLOGY, RABBIT

Sub acute and rangefinding studies:

134 085130, "Pynamin-Forte: Five Day Oral Toxicity Study in Female Rabbits (KT-91-0095)," (Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA., project # 1119-005, 7/17/89). Pynamin Forte (allethrin, 93.4% pure, lot #: 50310) was administered by gavage for 5 consecutive days at 0 (0.5% (w/w)

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methylcellulose), 30, 60, 125, 250, 500, and 1000 mg/kg/day to 5 virgin female Hra:(NZW)SPF rabbits per group. **No adverse effects** indicated. NOEL = 125 mg/kg/day (# deaths/group: 0/5, 0/5, 0/5, 0/5, 0/5, 4/5, and 5/5 at 0, 30, 60, 125, 250, 500, and 1000 mg/kg/day respectively. Tremors were reported at > 250 mg/kg/day. At ≥ 250 mg/kg/day a decreased food consumption with accompanying body weight decrease was observed.) **Supplemental** information. (H. Green & M. Silva, 9/14/90).

135 085131, "Pynamin-Forte: Range-Finding Teratology Study in Rabbits (KT-91-0096)", (Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA., Project # 1119-006P, 7/17/89). Pynamin Forte (allethrin, 93.4% pure, lot #: 50310) was administered by gavage on days 7 through 19 of gestation (day 0 = day of artificial insemination) at 0 (aqueous 0.5% (w/w) methylcellulose), 50, 100, 200, and 300 mg/kg/day to Hra:(NZW)SPF female rabbits (7/group). Maternal NOEL = 200 mg/kg/day (A significant decrease in food consumption on a g/kg basis was observed at 300 mg/kg/day.) Developmental NOEL ≥ 300 mg/kg/day (No fetal effects were observed at any dose). **No adverse effect indicated. Supplemental** to record # 085132 in volume 113-136. (H. Green & M. Silva, 9/18/90)

Teratology, rabbit:

136 085132, "Teratology Study in Rabbits with Pynamin Forte (KT-91-0097)", (Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA., project # 1119-006, 7/17/89). Pynamin Forte (allethrin, 93.4% pure, lot #: 50310) was administered by gavage on days 7 through 19 of gestation (day 0 = day of insemination) at 0 (aqueous 0.5% methylcellulose), 30, 100, and 350 mg/kg/day to Hra:(NZW)SPF artificially inseminated female rabbits (20/group). Maternal NOEL = 100 mg/kg/day (1 maternal death on gestation day 10 approximately 77 minutes postdosage with mydriasis, tremors, clonic convulsion, and lost righting reflex prior to death at 350 mg/kg/day. Necropsy revealed two 350 mg/kg/day does with gastric lesions.) Fetal NOEL = 100 mg/kg/day (Increased incidence--not significant--of fetal rib/rib-vertebral malformations at 350 mg/kg/day). **No adverse effects indicated below maternally toxic dose levels. **Acceptable.** (H. Green & M. Silva, 9/19/90).

GENE MUTATION

127 075939, "Reverse Mutation Test of Pynamin Forte in Salmonella typhimurium and Escherichia coli (KT-90-0083)", (Kogiso, S., Biochemistry and Toxicology Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, study # 1725, 2/13/89). Pynamin Forte (allethrin, 93.4% pure; lot #: 70202) was used in a reverse mutation assay with and without S9 (S-9 was obtained from male Sprague-Dawley rats induced with 500 mg/kg of Kanechlor-400) in duplicate with Salmonella typhimurium strains TA 100, TA98, TA1535, TA1537, TA1538 and Escherichia coli strain WP2uvrA at 0 (DMSO), 100, 200, 500, 1000, 2000, and 5000 µg/plate (limit test). **No increase in revertant colonies was observed. Acceptable. (H. Green & M. Silva, 9/25/90).

CHROMOSOME EFFECTS

**127 075940, "In Vitro Chromosomal Aberration Test of Pynamin Forte in Chinese Hamster Ovary Cells (CHO-K1)," (Kogiso, S., Sumitomo Chemical Co., Ltd., Osaka, Japan, study # 1729, April 1989). Pynamin Forte (allethrin, ≥ 91.9% pure, lot #: 70202) was used in a cytogenetic assay with CHO-K-1 cells (duplicate plates) at untreated, 0 (DMSO), 30, 60, 90, and 120 µg/ml (with S9

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from PCB (Kanechlor-400) induced male Sprague-Dawley rat livers) for a 2 hour exposure followed by harvest times at 18 or 24 hours. Cells with no S9 were incubated with untreated, 0 (DMSO), 5, 10, 15, and 20 µg/ml allethrin for 18 or 24 hours, then harvested (100 cells/duplicate culture/dose were scored for chromosomal aberrations). **No significant increase in number of chromosomal aberrations or frequency of cells with chromosomal aberrations was observed. Acceptable.** (H. Green & M. Silva, 9/27/90).

DNA DAMAGE

127 075941, "In Vitro Unscheduled DNA Synthesis (UDS) Assay of Pynamin Forte in Rat Hepatocytes", (Kogiso, S., Sumitomo Chemical Co., Ltd., Osaka, Japan, study # 1553, May 1989). Pynamin Forte (allethrin, ≥ 91.9% pure, lot #: 70202) was used in vitro in an unscheduled DNA synthesis assay (by autoradiography) in duplicate with male Sprague-Dawley rat hepatocytes at 0 (DMSO), 0.24, 1.20, 6.00, 30.00, and 60.00 µg/ml (50 cells scored/slide, 2 slides/dose). The test was performed twice. **No significant increase in unscheduled DNA synthesis was observed. Acceptable. (H. Green & M. Silva, 9/28/90).

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL STUDIES

These studies were not conducted with d-cis, trans allethrin (d-allethrin, pynamin forte)

018 933233 "Technical Bulletin: D-Trans Insecticidal Concentrate From MGK. Racemic Allethrin (which includes d-trans isomer)--Additional chronic toxicity of racemic allethrin," (No author's name included in the report. McLaughlin Gormley King Co., 3-80) A very brief summary of a two-year dog study with racemic allethrin at doses of 2000, 4000, 8000 or 20,000 ppm in the diet, 4/sex/group. Summary of a study published in 1965. Summary states the NOEL to be 4000 ppm based on mortality (1 male at 20,000 ppm and 1 male at 8000 ppm over 2 years) and body weight loss in 1 female at 8000 ppm. Summary states "No specific tissue damage attributable to treatment." Initially reviewed 7-2-85 by Apostolou as unacceptable with a possible adverse chronic effect based on mortality and body weight findings. Reconsideration of the summary indicates it has insufficient information for independent assessment but the effects noted in the initial review substantiate that the MTD probably was reached. **Unacceptable** (summary only). Luthra, 10/8/87 and Gee, 11/16/87.

TERATOLOGY, RAT

019 933396 "Esbiol Teratological Test Results: Effect on the Rat Fetus of Orally Administering Esbiol." (Roussel UCLAF, 2-75) Esbiol, no purity stated, given by oral gavage in olive oil to Wistar rats in a teratology study at 0.025, 0.05 and 0.1 ml/kg. Number per group is not stated. **Unacceptable.** Incomplete - tables and figures are not included. Number of rats per group is

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unclear. No data are included. Insufficient information for independent assessment of effects. **Possible adverse effect** indicated: the report states that "...transformation of lumbar into thoracic vertebrae..." was dose related. Apostolou, 7-2-85 and Gee, 11-12-87.

023 933397 "Teratology of D-trans Allethrin in Sprague-Dawley Rats, MGK (90% concentrate)." (Food and Drug Research Laboratories Inc., 4-20-79) D-trans-allethrin, 92.5% in corn oil, was given by gavage on days 6-15 of gestation to groups of 23 to 28 pregnant Sprague-Dawley rats at 0 (corn oil), 50, 125 or 195 mg/kg. Aspirin at 250 mg/kg was used as a positive control. An increase in skeletal abnormalities was observed at all levels. No appendices included. **Unacceptable** (incomplete, no analysis of dosing solution). Apostolou, 7-8-85. Findings changed to : skeletal abnormalities at 125 and 195 mg/kg dose levels. Developmental NOEL = 50 mg/kg. Maternal NOEL = 125 mg/kg. Luthra 10/87.

TERATOLOGY, RABBIT

013 933395 "Teratology Study - Rabbits (Pynamin) - Final Report." (Hazleton Labs, 6-19-72) Allethrin, assumed 100% purity, was given by gavage on days 6-18, to groups of New Zealand White rabbits, 12 to 15/group, at 0 (corn oil), 215 or 350 mg/kg. NOEL $\geq$ 350 mg/kg (HDT). **Unacceptable.** Half of the does delivered naturally. Dosage selection not justified, high mortality. **No adverse effect indicated.** Apostolou, 7-8-85 and Luthra. 11-12-87.

GENE MUTATION

023 033561 "Detection of a Mutagenic Potency of Bioallethrin: Microbial Assays - Ames Test Using S. typhimurium." (Roussel UCLAF, 12-27-79) Salmonella typhimurium, strains TA1535, TA1537, TA1538, TA98 and TA100 were used to test Allethrin at 0 (DMSO), 2, 10, 50, 200, 500, 1000, or 5000 ug/plate, with and without activation (4 plates per concentration). **No adverse effect indicated. Unacceptable.** No characteristics of test material. No cytotoxicity by decrease in spontaneous revertants to verify exposure to a.i. and no analysis of the test material. Apostolou, 7-8-85.
Note: According to documents in 104, as of 1986, EPA had not approved of grouping allethrin with Bioallethrin.

106 052476 "Mutagenicity of Allethrin in Bacterial Systems". (Sumitomo Chem. Co., Osaka, Japan, 10/25/79). Allethrin, 91.8% purity, tested for gene mutation in Salmonella typhimurium strains TA98, TA100, TA1535, TA1538 @ 0, 10, 50, 100, 500, 1000, 5000 ug/plate (±S9), preincubation for 20 minutes before plating. **No adverse effect indicated. Unacceptable:** no individual plate counts, no cytotoxicity; inadequate description of methods. **Upgradeable.** Luthra, 10/87.

CHROMOSOME EFFECTS

023 033563 "Detection of a Mutagenic Potency of Bioallethrin: Micronucleus Test in Mouse." (Roussel UCLAF, 12-27-79) Allethrin was given to Swiss CD1 mice by gavage, 2 doses at 24 hour intervals, 5/sex/dose, at 0 (sesame oil), 100, 200 or 400 mg/kg. Sacrificed at 6 hours after second dose. **No adverse effect indicated. Unacceptable** Scoring criteria not included, no test material characterization, unacceptable sacrifice interval. Also, see note under 033561 above. Apostolou, 7-8-85 and Gee, 11/13/87.

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106 052522 "In vivo chromosomal Aberration Test of Allethrin in Mouse Bone Marrow Cells." (Sumitomo Chemical Co., Osaka, Japan, 4/18/80). Allethrin, 91.1% purity tested for in vivo chromosomal aberrations at 0, 500, 800, or 1000 mg/kg in 6 male mice per dose; sacrificed at 24 hours. **Unacceptable:** Insufficient number of animals; Males only used without justification; MTD not demonstrated; data incomplete. **No adverse effect indicated. Not upgradeable.** Luthra, 10/87.

106 052477 "In vitro sister chromatid exchange test of Allethrin" (Sumitomo Chem. Co., Osaka, Japan, 12/20/79). Allethrin, 91.1% purity, tested 3 hrs. in vitro for SCE in primary mouse embryo cells @ 0, 10^{-5}, 5 x 10^{-5}, 10^{-4} M per dish. Scored at 36 hrs. **Unacceptable:** no individual data. Incomplete protocol. **No adverse effect indicated. Upgradeable.** Luthra, 10/8.

DNA DAMAGE

023 033562 "Detection of a Mutagenic Potency of Bioallethrin: Microbial Assays - Growth Inhibition Test Using E. coli." (Roussel UCLAF,12-27-79) This is a summary report of a growth inhibition test by well diffusion using E. coli. **No adverse effect indicated. Unacceptable.** Apostolou, 7-8-85.
See note under 033561 above. Gee, 11/87.

106 052580 "Mutagenicity Test of Allethrin in Bacterial System" (Sumitomo Chem. Co., Osaka, Japan, 10/25/79). Allethrin, purity 91.8%, tested for DNA damage in B. Subtilis M45 (rec^+)/H17 (rec^-) @ 50, 150, 500, 1000 & 5000 ug/paper disk. **Unacceptable:** no cytotoxicity = no test, activating system not used, dosage not justified, data incomplete. **No adverse effect indicated. Not upgradeable.** Luthra, 10/87.

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