CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE

MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

EPTC

SB 950-049, Tolerance # 117

August 8, 1986
Revised October 9, 1986
Revised August 4, 1987
Revised November 8, 1988

I. DATA GAP STATUS

Combined (chronic + onco) rat: No data gap, possible adverse effect (chronic)

Chronic dog: No data gap, possible adverse effect

Onco mouse: No data gap, no adverse effect

Repro rat: No data gap, no adverse effect.

Terato rat: Data gap, possible adverse effect indicated.

Terato rabbit: No data gap, no adverse effect.

Gene mutation: No data gap, possible adverse effect.

Chromosome: No data gap, possible adverse effect

DNA damage: No data gap, no adverse effect.

Neurotox: No data gap, possible adverse effect (not acute delayed neuropathy.)

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name T881108, revised November 8, 1988
Toxicology Summary revised by J. Parker and J. Gee based on reviews by J. Gee and J. Parker

J. Parker 11/14/88
J. Gee 11/14/88

II. TOXICOLOGY SUMMARY

024 270 "Guidance for the Reregistration of Pesticide Products Containing EPTC as the Active Ingredient." (USEPA, September 30, 1983)

COMBINED, RAT

** 032 026949 "Two Year Oral Toxicity/Oncogenicity Study in Rats." (9/30/83, IRDC.) EPTC (lot CHK-0601, 98.6% by weight) was fed to 60/sex/group at 0, 5, 25 or 125 mg/Kg in diet over two years; diets analyzed periodically; several compound related effects at 125 mg/Kg and to a lesser extent at 25 and 5 mg/Kg; NOEL: < 5 mg/Kg/day in males for muscle atrophy/degeneration and 5 mg/kg/day in females; adverse effects include cataracts, neuromuscular atrophy and degeneration, external testes and possibly chronic myocarditis; acceptable with a possible adverse effect.

	Males (mg/kg)				Females			
Observation	0	5	25	125	0	5	25	125
Number	46	49	47	39	47	46	50	43
Muscle: atrophy	1	0	22	36	0	0	3	34
Degeneration	0	5	9	1	0	3	10	0

JG, 10/7/85.

037, 038, 039 34467, 34468, 34469 Addenda (individual data) to 26949.

018 935176 Interim report for 26949.

** 069 055491 (10 volumes) "Two Year Oral Feeding Study of the Oncogenicity and Chronic Toxicity of EPTC in Rats." (Hazleton Labs America, 3/20/87, Study No. 6100-106) EPTC, technical, Lot No. 518-996, 98.4%; fed in the diet at 0, 9, 18, 36 or 72 mg/kg/day with periodic adjustments in the ppm to maintain the nominal doses; 90/sex/group of Crl:CD(SD)BR rats; NOEL in males not established, NOEL in females = 9 mg/kg/day (decreased body weight gain, skeletal muscle atrophy and nerve changes especially in hind quarters, slight increase in degenerative cardiomyopathy; possible adverse effect (hindquarters muscle syndrome). The incidence of HMS appeared in males at earlier times as the dose increased and the incidence was dose related in both males and females. The occurrence of cataracts in treatment groups versus controls was not as clear. Acceptable. RAM, 5/4/87 and JG, 6/4/87.

	Males (mg/kg/day)					Females				
Observation	0	9	18	36	72	0	9	18	36	72
Hindquarter muscle syndrome	1	6	27	45	62	0	0	3	26	48
Mean week at onset	99	100	95	82	72.5	-	-	84	87	82
Paralysis of limb	2	0	0	0	0	0	0	0	0	0

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CHRONIC, DOG

** 053, 054 46264, 46265 "One-year Oral Feeding Study of the Chronic Toxicity of EPTC in Dogs." (6/10/86, Hazleton.) EPTC, 98.4% (lot 518-996); fed in the diet at 0, 200, 600 or 1800 ppm for one year; 6/sex/group; NOEL not clearly established but ≥ 1800 ppm; no adverse effect. No findings in the heart were reported upon necropsy or microscopic exam. Emesis was slightly increased in severity at the high dose over the test period. This study was initially reviewed as unacceptable because the selection of doses was not justified and the subchronic study, Record No. 50734, was not on file. With the submission of the subchronic, the study is upgraded to acceptable with the comment that the high dose was marginal in showing any adverse effect.
JG, 10/7/86 and 8/3/87.

066 50734 "A Three Month Subchronic Oral Toxicity Study of EPTC in Beagle Dogs." (Bio/Dynamics, Inc., 2/15/85, Project No. 83-2781) EPTC, 98.4%; fed in the diet to 6/sex/group at 0, 200, 600 or 1800 ppm for 3 months; no adverse effect reported and NOEL ≥ 1800 ppm. Submitted as justification for the selection of doses in the one-year study, Record numbers 46264 and 46265. RAM, 5/5/87 and JG, 6/3/87.

** 077 065928 "One-Year Oral Toxicity Study with Eptam Technical in Dogs; Final Report." (Stauffer Chemical, CT, 9/8/87, T-12712) Eptam technical, 97.6% by weight; tested at 0, 1, 8 or 60 mg/kg/day by capsule with 5 beagle dogs/sex in control and high dose groups and 4/sex in low- and mid-dose groups; NOEL = 8 mg/kg/day (body weight, cholinesterase inhibition, neuropathology at 60 mg/kg with 1 male sacrificed day 84 due to toxicity). Neuropathology described as Wallerian degeneration of the spinal cord (multiple sites) and peripheral nerves with males more affected than females. In addition, bile stasis was increased in incidence at 60 mg/kg and was considered potentially treatment-related. Acceptable. Gee, 7/20/88,

SUMMARY: Both studies in the dog were evaluated as acceptable but with different conclusions about adverse effects. Although both studies used the oral route, the study at Hazleton fed the EPTC in the diet with a maximum of 1800 ppm which was marginally toxic. The study by Stauffer gave the EPTC by capsule and used 60 mg/kg/day as the high dose - estimated as approximately 2400 ppm based on 1 mg/kg/day equivalent to 40 ppm in the diet. Since this dose was higher than that used by Hazleton and was administered all at one time, the conclusion is that EPTC treatment resulted in a possible adverse effect. Gee, 11/8/88.

ONCOGENICITY, RAT

See under combined rat.

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JG 11/14/88
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ONCOGENICITY, MOUSE

018 935172 "Lifetime Oral Study in Mice." (12/22/78, IRDC.) EPTC technical grade, three lots; fed to 60/sex/group, CD-1 mice, at 0, 5, 20, or 80 mg/Kg in the diet for two years; NOEL not clearly established because high dose showed marginal effect on blood parameters with no MTD; no oncogenic effects reported; unacceptable (test material not described, doses not justified, muscle and sciatic nerve were not examined microscopically), possibly upgradeable. Note that this report was judged as acceptable 3/20/85 but rereview found the study was missing some necessary data. JG, 3/20/85 and 10/7/85.

040 34470 Addendum (individual data) for 935172.

** 049-052 45704 - 07 "Oncogenicity Study in Mice with EPTC, Study no. 6100-104." (5/15/86, Hazleton.) EPTC, lot 518-996, 98.4%; fed to 60/sex/group, CRL:CD-1 mice, at 0, 200, 600 or 1800 ppm for 73 weeks; NOEL = 200 ppm based on lower body weights and lower food intake; no oncogenic effect; no adverse effect reported; no findings in muscle or sciatic nerve; Acceptable. JG, 10/8/86

Comment on long-term feeding studies in rats, dogs and mice: The adverse effects on nerve and muscle in the rats in two studies conducted for two years was confirmed in one dog study conducted over a one-year period but not in the mouse at 73 weeks. In the rat, the effect did not appear until late in the study. In the dog study by Stauffer, degeneration of the spinal cord and peripheral nerves and skeletal muscles was reported. In the second mouse study, Record # 935172, which lasted two years, the skeletal muscle and sciatic nerve were not included in the list of tissues examined histologically but no behavioral effect was reported. Gee, 11/8/88.

REPRODUCTION, RAT

018 935174 (5/12/75, Woodard Research Corp.) Eptam technical, five male and 15 female Sprague-Dawley rats were fed 32 mg/kg/day starting 3 days before mating. Not by standard protocol, unacceptable, not upgradeable. Insufficient information to evaluate. JG, 3/21/85.

** 018 935175 "A Two-Generation Rat Reproduction Study with Eptam Technical." (10/8/82, Stauffer, T-10123) EPTC (98.6%) tested at 0, 40, 200 and 1000 ppm in the diet; two generations with two litters per generation; 15 males and 30 females per group; NOEL = 200 ppm (parental body weight and pup weights); no repro effects reported; necropsy on all parental animals. Acceptable with 46266-71 below. JG, 10/7/85
EPA one-liner: core grade of Supplementary. NOEL = 200 ppm based on decreased parental body weights and food intake at 1000 ppm (HDT). No histopathology data on reproductive tissues or target organs. [Review date of EPA is not clear.]

036 34465 Addendum (individual data) to 935175.

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036 34466 Duplicate of 935175.

** 055 to 060 46266 - 71 "Two-Generation Reproduction Study with EPTC in Rats." (6/9/86, Hazleton, Study 6100-108) EPTC, lot. 518-996, 98.4% purity; fed at 0, 50, 200 or 800 ppm in the diet to 30/sex/group, for 10 weeks before mating for 2 generations; no adverse reproductive effect on parental animals; significantly reduced pup weights at 800 ppm in F1a pups and F2a pups; parental body weights were also reduced at these doses; all F_0 parents given a gross and microscopic exam of gonads and selected tissues; Reproductive NOEL = 800 ppm (HDT); systemic NOEL = 50 ppm. Report states NOEL to be 200 ppm. Note: Although not a reproductive effect, the incidence of cardiomyopathy was increased in F_1A adults at termination in a dose-dependent manner. Acceptable.

	Males (ppm)				Females			
Observation	0	50	200	800	0	50	200	800
Cardiomyopathy	4/23	3/24	15/25	25/25	1/25	0/24	5/25	25/25

JG,10/8/86.

TERATOGENICITY, RAT

035 034463 "A Teratology Study in Rats with Eptam." (11/3/83, WIL Research, WIL-27013.) EPTC (considered to be 100% pure, lot CHK 0601, 98.6% by weight); tested at 0, 30, 100, or 300 mg/Kg in corn oil vehicle on days 6-15 of gestation by gavage to 25/group; COBS-CD rats; females C-sectioned 22 (0 mg/Kg), 19 (30 mg/Kg), 21 (100 mg/Kg) and 6 (300 mg/Kg); maternal mortality and toxicity at 300 mg/Kg; some embryotoxicity at 100 mg/Kg (increased resorptions at 100 and 300 mg/kg/day, decreased fetal weight at 300 mg/kg); NOEL = 30 mg/Kg for developmental toxicity; NOEL = 100 mg/Kg for maternal tox.; initially evaluated as acceptable but since no analyses of dosing solutions were performed, the study is downgraded to unacceptable but upgradable with the submission of the analyses; possible adverse effect. JG, 10/4/85 and 8/3/87 and JAP, 8/4/87.

071 060524 Supplement to 034463 Characterization of Technical Eptam Lot CHK 0601. This document identifies the impurities in the technical grade. CDFA needs analyses of dosing solutions or a retrospective analysis accompanied by copies of the laboratory notebooks showing the correct weights of active ingredient. No worksheet prepared. No change in study status. Parker 11-8-88.

044 039607 "Effect of EPTC on Pregnancy of the Rat." (11/6/85, Huntingdon Res. Centre.) EPTC (98.4%), batch no. 518996; Crl:COBS CD (SD) BR rats; tested at 0, 30, 100 and 300 mg/Kg in 1% methylcellulose by gavage days 6-15 of gestation to 25/group; analyses of dosing solutions and stability included; maternal and developmental NOEL: > 300 mg/Kg; Unacceptable (MTD not achieved), not upgradeable. JAP, 4/25/86.

066 051092 Supplement to 039607. Summary table of maternal findings and rebuttal. No worksheet prepared. No change in study status. Gee and Parker 8-4-87.

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SUMMARY: The difference in study results may be attributed to a difference in source of animals, difference in purity and source of compound tested and most important, difference in the vehicle used. In study 034463 there were 14 of 25 animals at 300 mg/kg/day found dead or killed in extremis. No cholinergic signs were noted. In study 039607 all dose levels were stated to cause salivation. However no other clinical signs were noted, such as unsteady gait or hyper-reactivity, which usually accompany salivation. The report does not state if the salivation was seen post-dosing. Since the results of these studies are so different, the lack of analysis of dosing solutions for study 034463 becomes especially important. CDFA considers there to be a data gap for rat teratology with a possible adverse effect noted in study 034463. JG and JAP, 8/4/87 and 11-9-88.

TERATOGENICITY, RABBIT

** 045 39608 "Effect of EPTC on Pregnancy of the Rabbit." (10/10/85, Huntingdon Res. Centre.) EPTC (98.5%), batch 518996; tested at 0 (1% methylcellulose), 30, 100 and 300 mg/Kg by gavage to 16-18 per group on days 6 through 18 with day of mating = day 0; New Zealand White rabbits; maternal toxicity NOEL = 300 mg/kg, MTD not reached - however, a preliminary study had cholinergic signs at 350 mg/kg/day; developmental toxicity NOEL: < 30 mg/Kg, malformations noted in all treated groups; acceptable. JAP, 4/25/86.

066 051091 Historical control data for 39608 and rebuttal. No change - the possible adverse effect remains. Gee and Parker, 8-4-87.

** 076 065927 "A Teratology Study in Rabbits with Eptam Technical." (Stauffer Chemical Company, CT, 8-12-87, T-12982) Eptam Technical, 97.6%, administered by gavage at 0 (corn oil), 5, 40, or 300 mg/kg/day to 16-18 mated NZW rabbits/dose level on days 7-19 of presumed gestation. Maternal NOEL = 40 mg/kg/day (decreased body weight gain, cholinergic signs and decreased serum and RBC cholinsterase). Developmental NOEL = 40 mg/kg/day (decreased fetal weight). Acceptable, No Adverse Effect. Parker 11-7-88.

SUMMARY; The fetal malformations seen in the HRC study (#39608) were not confirmed in the subsequent study conducted at Stauffer (#065927). Differences may be due to different vehicles and source of animals. In looking at the collective data, the evidence for a developmental effect is weak. Since in the Stauffer study there was no indication of fetal changes similiar to those seen in the HRC study, and maternal cholinesterase was decreased both statistically and biologically at 300 mg/kg/day, CDFA considers there to be no indication of an adverse effect. **Thus the rabbit teratology data gap is filled and no adverse effect is indicated.** Parker 11-8-88.

TERATOGENICITY, MOUSE

018 935173 (4/6/67, Woodward Research Corp.) EPTC, 97.8%; Unacceptable (major variances from guidelines), not upgradeable. Twenty

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females were fed 0, 8 or 24 mg/kg/day of 97.8% EPTC. No justification of dose or evidence of toxicity. JG, 3/21/85
EPA one-liner: Core grade of invalid. Non-gavage study and data on actual intake of test material. Only 7, 8 and 6 pregnant animals. Only 2 doses with data under reported.

035 34464 Duplicate of 935173.

MUTAGENICITY, GNMU

Microbial systems

018 935178, 31727 "Mutagenicity Evaluation of Eptam Tech 3905-35, Final Report." (Litton Bionetics, 10/77, project no. 20838.) EPTC, purity not stated; tested in Salmonella at 0, .001, .01, .1, 1.0 and 5.0 ug/plate with and without activation; TA 1535, TA 1537, TA 1538, TA 98, and TA 100, single plate per strain; unacceptable (no replicates and no good evidence for activity of S9 fraction), not upgradeable. Also includes Saccharomyces D4 (# 31727). No increase in reversion rate reported. JG, 3/21/85

018 31728, 31729 "Mutagenicity Testing on EPTC in Microbial Systems." (7/24/78, Institute of Environmental Toxicology,) EPTC (97.2%) tested at 0, 10, 50, 100, 500, 1000, and 5000 ug/plate in Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100 with and without metabolic activation; unacceptable (no replicate trial); not upgradeable. No increase in reversion rate reported. Also tested E. coli WP2 hcr strain. JG, 3/21/85.

018 935180 "Evaluation of Herbicides for Possible Mutagenic Properties." (1972, publication in J. Agr. Food Chem. 20: 649) 110 Pesticides including EPTC; "-" for activity in Salmonella; unacceptable with insufficient information. JG, 3/21/85.

Mammalian cells

** 032 26946 "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test: Forward Mutation Assay." (9/17/84, Stauffer.) EPTC (98.6%, lot 4921-4-10) tested at 0, 0.005, 0.01, 0.02, 0.04 and 0.06 ul/ml on mouse lymphoma (L5178Y) cell + rat liver S9; 0.0125, 0.025, 0.05, 0.1 and 0.15 without S9; in presence of S9, test article induced moderate increase in mutation frequency; two trials. At 0.06 ul/ml, mutation frequency per 10^6 was 105 in trial 1 and 158 in trial 2 compared with 31 for solvent controls. Acceptable.. JG, 10/8/85.

047 42779 "Mouse Lymphoma Cell Mutagenesis Assay (TK+/- to TK-/-) of EPTC." (2/18/86, SRI International.) EPTC (98.5%, lot 528-995), in mouse lymphoma (L5178Y) cells, tested at 0, 42, 60, 86, 123, 175, and 250 ug/ml with rat liver activation and 0, 118, 131, 145, 162, 180 and 200 ug/ml without activation; 2 or 3 cultures for each concentration; one trial only; no increase in mutation frequency (MF) without activation; with S9 activation, MF increased to 487 and 521 at 175 and 250 ug/ml compared with 86 for solvent control. Unacceptable (single trial). JG, 10/6/86.

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Summary: The data gap for gene mutation is filled. Comparison of the two studies in mammalian cells (36946 and 42779) shows that EPTC treatment gave comparable results -- no observable increase without activation and about a 3-fold increase with activation. Concentrations used in the second study were somewhat higher than in the first. **The data gap is filled with a possible adverse effect.** Gee, 11/8/88.

MUTAGENICITY, CHROMOSOME

** 032 26947 "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test: Cytogenetic Assay." (9/17/84, Stauffer.) EPTC (98.6%) tested at 0, 0.005, 0.01, 0.02, 0.04 and 0.06 ul/ml on mouse lymphoma (L5178Y TK+/-) cells with activation and 0.0125, 0.025, 0.05, 0.10 and 0.15 ul/ml without activation; exposed 4 hours, resuspended in Budr for 20 hours; 50 cells per culture were scored. Increased aberrations at 0.025 ul/ml and increased aneuploidy at 0.01 ul/ml without activation -- neither finding was concentration dependent; initially reviewed as unacceptable based on no repeat experiment to confirm the possible adverse effect and not upgradable. Reconsideration upgrades the study to acceptable status as a confirming repeat is not essential with this test type. JG, 10/7/85 and 8/4/87.

032 26948 "Mutagenicity Evaluation in Bone Marrow Micronucleus." (11/28/84, Stauffer.) EPTC (98.6%, Lot 4921-4-10) tested at 0, 250, 500, and 1000 mg/Kg (trial 1, single dose) or 1000, 1200 and 1400 g/Kg (trial 2, two doses at 24 hours) by gavage in a micronucleus assay using CD-1 mice (both male and female); animals were sacrificed at 24, 48 and 72 hours; increase in micronuclei/1000 PCE in the first, but not the second trial; Unacceptable (need individual data on micronuclei/1000 cells, CP control questionable, vehicle controls for females are high compared to males in trial 1 and for both males and females in trial 2, high mortality in trial 2, results of trial 2 vary considerably from those of trial 1), possibly upgradeable. JG, 10/7/85.

** 047, 048 42777 "Clastogenic Evaluation of EPTC Technical, 518-996, BR85-40, in an in vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells." (11/85, Litton Bionetics.) EPTC (lot 518-996, 98.4%) was tested in duplicate in Chinese hamster ovary (CHO) cells at 0, 15, 30, 75 or 150 ug/ml with rat liver activation (2 hours) and at 0, 30, 60, 90 or 120 ug/ml without activation (17.5 hours); no increase in chromosome aberrations is reported; acceptable. JG, 10/6/86.

Summary: The two chromosomal aberration studies have conflicting results -- reconsideration of the results with mouse lymphoma, in view of the later study, make the biological significance questionable. The study did not show a dose-related response for either aberrations or aneuploidy. The micronucleus effect, however, is still unresolved for a possible adverse effect. **The data gap is filled with a possible adverse effect.** Gee, 11/8/88.

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MUTAGENICITY, DNA

018 935179 "Mutagenicity Testing on EPTC in Microbial Systems." (7/24/78, Institute of Environmental Toxicology.) EPTC (97.2%) tested at 0, 1, 5, 10, 25, 50, and 100 % V/V in B. subtilis (strains M 45 and H17); disk assay; unacceptable (no repeat experiment, no activation included and other major variances from guidelines), not upgradeable. JG, 3/21/85.

030 26945 "Effects of EPTC on Human Fibroblast DNA." (9/19/84, Stauffer.) EPTC (98.6%, lot 4921-4-10) tested on human skin fibroblast DNA; no effects reported; unacceptable (insufficient protocol for evaluation), Two tests were run: 1) cells were treated 30 min and the DNA sized on alkaline sucrose gradients and 2) DNA was nick translated with E. coli pol I and radioactive dCTP with DNA collected on filters. JG, 10/8/85.

** 047, 048 42778 "Evaluation of the Potential of Ethyl-(N,N-dipropyl)thiocarbamate to Induce Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures." (1/86, SRI International.) EPTC, lot 518-996, 98.5%; primary rat hepatocytes tested for unscheduled DNA synthesis at 0, 0.1, 0.5, 1.0, 3.0, 5.0, 30, 50, 100, 250, 500, 1000 or 5000 ug/ml, 19-21 hours with ^{3}H-thymidine; no increase in UDS is reported; acceptable. JG, 16/6/86.

NEUROTOXICITY

031 26950 Acute Delayed Neurotoxicity Study with Technical EPTAM in {adult Hens." (2/5/81, Stauffer.) EPTC (98.6%, lot CHK 0601) treatment on days 1 and 22 at 7200 mg/Kg; 12 hens in negative and positive control groups, 16 in treatment group; test article caused mortality of 6/16; 4/10 survivors showed some bilateral degeneration of the sciatic nerve, but no brain or spinal cord lesions different from controls; Marek's disease in all; unacceptable (no individual data), upgradeable. A more recent study (see below) does not report an adverse finding but the dose was lower by 35%. Study 26949 in rats (see above) indicated neuromuscular atrophy and degeneration due to EPTC. JG, 10/9/85.

** 034 32736 "Acute Delayed Neurotoxicity Study with EPTC Technical in the Domestic Hen." (12/28/84, Huntingdon Research Centre.) EPTC, 98.4%; forty hens dosed at 4674 mg/Kg, 10 hens in both positive and negative control groups; 4674 mg/Kg the calculated LD_{50}; no evidence of acute delayed neurotoxicity; initially reviewed as unacceptable (not all hens subjected to histopathology (10/31 selected), no atropine protection and in view of data in record #26950, dose may not be high enough)but possibly upgradeable.
With submission of the rebuttal in 117-066, the question of how the hens were selected for histopathology has been answered. Also, as pointed out, the dose of 4674 mg/kg is close to the limit test of 5000 mg/kg. The study has been upgraded to acceptable status. JG, 10/4/85 and 8/3/87.
EPA: Guideline.

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