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

013870

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

November 18, 1999

SUBJECT: Malathion: Study Pathologist's Responses (MRIDs 44837001; 44970601; 44970501) to Health Effects Division's Questions on the Nasal Tissue Histopathology Re-evaluation (MRID 44782301) of the Combined Chronic Toxicity/Carcinogenicity Study in the F344 Rat (MRID 43942901).

FROM: Brian Dementi, Ph.D., D.A.B.T.
Toxicology Branch I
Health Effects Division (7509C)

Brian Dementi 11/18/99

THRU: Alberto Protzel, Ph.D.
Senior Branch Scientist
Toxicology Branch I
Health Effects Division (7509C)

Alberto Protzel 12/1/99

TO: Patricia Moe
PM Team 53
Special Review and Reregistration Division (7508W)

TO: Paula Deschamp
Risk Assessor
Reregistration Branch 2
Health Effects Division (7509C)

Registrant:	Cheminova Agro A/S	Submission Nos:	S569531; S569540; S569558
Chemical:	Malathion	P.C.Code:	057701
Case No.:	818961		
DP Barcode:	D260115; D260116; D260120		
MRID Nos:	44837001; 44970601; 44970501		

In the process of reviewing the histopathology re-examination of nasal tissues (MRID 44782301)

(1)

submitted by the registrant in response to HED's Cancer Assessment Review Committee's request for such re-examination, further information was sought from the registrant. Specifically, it was noted that in the original study submission of the two-year study (MRID 43942901), the diagnosis for male rat #5040 from the high dose study group as identified in nasal/turbinate section 2 was "nasal mucosa (olfactory): carcinoma" (p. 4100)(copy appended); however, for this same slide, the diagnosis by the same study pathologist, Dr. Henry Bolte, as submitted to Dr. James Swenberg in the re-examination (MRID 44782301) was "nasal mucosa (respiratory): epithelium-hyperplasia, multi-focal, slight" (p. B-1191)(copy appended), while Dr. Bolte's diagnosis for nasal/turbinate section 1 (a new slide not obtained in the original study) was "nasal mucosa (respiratory): adenoma" (p. B-1190) So for this rat, it remained that a neoplasm was identified in the nasal turbinates, but the character of that neoplasm was revised by the Study Pathologist from carcinoma of the olfactory epithelium in section 2, to that of adenoma of the respiratory epithelium of section 1, with no tumor finding in section 2. When the reviewing pathologist, Dr. Swenberg, examined section 2, he identified an adenoma, which the two pathologists agreed extended from section 1 into section 2. Dr. Swenberg also perceived the same tumor extending into section 3 (another new tissue section prepared for the re-examination), with Dr. Bolte agreeing. The latter individual had not reported the finding in his original diagnosis of section 3. Dr. Swenberg concurred with Dr. Bolte's diagnosis in section 1.

In view of the above findings, Dr. Dementi sought clarification via an April 14, 1999 phone conversation with the registrant's representative, Jellinek, Schwartz and Connolly, Inc. The question posed was: what explains the Study Pathologist's change of diagnosis from the original carcinoma of the olfactory epithelium in section 2, to a diagnosis which describes no tumor finding in section 2, to that of adenoma of the respiratory epithelium of another section. The response to that question as we have received it in the April 19 letter of Dr. Bolte (MRID 44837001) (copy attached) reads in part as follows: "When only sections from Levels 2 and 4 were available, a fragment of a neoplasm obviously originating from the respiratory epithelium, was seen in the nasal lumen. However, when additional sections were cut, this neoplasm was seen to be attached to the respiratory mucosa on level 1 and was identified to be an adenoma of respiratory epithelium." Further along, Dr. Bolte says: "At the time of the original reading (prior to that for the peer review) this neoplasm was categorized as a carcinoma of the *respiratory epithelium* (emphasis added), however, when the site of attachment was found, the neoplasm could be more appropriately evaluated and the diagnosis was changed to adenoma of respiratory epithelium." In this latter statement, Dr. Bolte's characterization of the tumor in question as being of the respiratory epithelium in the original reading is not consistent with the origional reading as reported in the origional study submission (MRID 43942901) (p. 4100).

It remains a curiosity in the mind of this reviewer as to why the tumor was originally identified as a carcinoma, and why of the olfactory epithelium.

Another question posed in the April 14 phone call concerned the diagnosis of the neoplasm in female rat #5503, from the high dose group. In the original study submission, the neoplasm was

diagnosed as "squamous cell carcinoma arising from the squamous epithelium lining the alveolus of a tooth" (p. 5062) (copy appended), yet in the report submitted to Dr. Swenberg, the diagnosis for the same nasal tissue section read "palate: squamous cell carcinoma"(p. B-2237) (copy appended). In responding to the April 14 question, in his April 19 letter, Dr. Bolte says: "During my original evaluation of level 4 of the nasoturbinal tissues from the animal, I concluded that the squamous cell carcinoma may have originated from a tooth alveolus. During the peer review with Dr. Swenberg, we discussed the origin of this neoplasm and jointly concluded that the site of origin was the palate adjacent to the tooth." This response is clear except that on reading the report of the re-analysis written by Dr. Swenberg, one is led to the conclusion that the diagnosis of squamous cell carcinoma of the palate was the diagnosis submitted by the Study Pathologist to the Reviewing Pathologist prior to the latter's examining the slides. In other words, the diagnosis appears to have been revised prior to any discussions between the two pathologists, if this reviewer understands the submission correctly.

In view of uncertainties concerning the changes of diagnoses as discussed, additional more detailed descriptions of procedures followed in the re-examination were requested in the April 14 phone conversation. Specifically, were new slides for sections 2 and 4 for male rat #5040 possibly obtained along with sections 1, 3 and 5, that might explain differing diagnoses from the very original? Dr. Bolte has answered this question in his April 19 letter, saying the original slides from sections 2 and 4 were retained and not re-cut.

Upon further consideration of the results of this nasal tissue histopathology re-evaluation and peer review, and in consideration of the oral cavity tumors that were identified in the nasal tissue re-evaluation, additional clarification was sought from the registrant concerning the extent of the pathology evaluation of oral cavity tissues. Accordingly, in response to a July 19 request from Dr. Dementi, Ms Patricia Moe, product manager, requested the additional information from the registrant by phone conversation with Mr. Paul Whatling on July 21. A response provided by Dr. Bolte dated August 11 (copy appended)(MRID 44970600), was received officially under the September 30 cover letter of Mr. Blane Dahl to Ms Moe. In his response, Dr. Bolte indicated that all cavities, oral cavity included, received postmortem examinations for macroscopic abnormalities, and that the tissues associated with the oral cavity included the lips, gingiva, teeth, buccal mucosa, tongue and hard palate.

Dr. Bolte also provided additional historical control data for oral cavity neoplasms. In reference to the data base from the performing laboratory, Huntington Life Sciences, Dr. Bolte says: "Inhalation studies were selected since oral tissues are also examined with the nasoturbinal tissues. Four recent studies had 453 unexposed, control rats (227 males, 226 females). A squamous cell carcinoma arising from a tooth alveolus occurred in 1/227 males and a fibrosarcoma arising from peridontal tissue occurred in two rats, 1/227 males and 1/226 females. The rare occurrence of squamous cell carcinomas and fibrosarcomas are usually sequellae to peridontal disease. Peridontal disease, uncommon in aging and aged rats, is characterized by the presence of impacted food particles, inflammation ranging from acute to chronic, fibrosis and hyperplasia of the squamous epithelium lining the tooth alveolus. The severity of peridontal

disease is variable and on occasion it can be severe with extensive squamous cell hyperplasia." We should note at this point that peridontal disease was not uncommon in the malathion combined chronic toxicity/carcinogenicity study, but occurred in all groups. Dr. Bolte also provides historical data for CD and Fischer 344 rats. Squamous cell tumors of the oral cavity are demonstrated to be very rare. Accordingly, the following incidences were provided. For CD rats: "Squamous cell carcinoma-hard palate: 1/1686 males. Squamous cell carcinoma-site not specified: 1/1686 males and 3/1691 females. Papilloma: lip: 1/1691 females."

For Fischer F344 rats (citing the NTP data base, 1990). "UNTREATED RATS: Squamous cell papilloma-site not specified: 1/1936 males, 1/1983 females. Squamous cell carcinoma-site not specified: 1/1936 males, 1/1983 females." "CORN OIL GAVAGE: Squamous cell papilloma-site not specified: 6/1949 males, 6/1950 females. Squamous cell carcinoma-site not specified: 0/1949 males, 0/1950 females."

In response to this submission, and at the request for still further clarification from this reviewer, Patricia Moe forwarded additional questions to the registrant in her letter of September 22, 1999, to which Dr. Bolte responded via his letter of September 28 (copy appended)(MRID 44970501) submitted to the Agency under the September 30 cover letter of Blane Dahl.

Specifically, Dr. Bolte provided assurances that oral cavity tissues in question were examined macroscopically, but he advised that the oral cavity is not a protocol tissue. "Non-protocol tissues were listed only if macroscopic findings were noted, even if only one animal. Numerous tissues, including those associated with the oral cavity, not protocol required, were examined per Standard Operating Procedure (SOP); if there were no macroscopic findings, these tissues were not included in the incidence summary of macroscopic findings." We therefore conclude there were no *macroscopic* findings of the various tissues that constitute the oral cavity.

Dr. Bolte also affirmed that the nasal adenoma of male rat #5040, a neoplasma identified in the peer review as seen in nasal/turbinate sections 1,2 and 3, was not seen macroscopically. "Based on microscopic examination, the adenoma in the nasoturbinal tissues was very small. Due to its small size, it was unlikely that it would have been seen when examined macroscopically at the time that the nasoturbinal tissues were trimmed for processing toward microscopic evaluation." We understand from this that macroscopic examination of the nasal cavity occurs not before but during preparation of tissues for microscopic examination, and that this procedure may somewhat compromise macroscopic detection. Also, though the adenoma in question spanned three nasoturbinal sections, we acknowledge the possibility of its being of slender geometry which could explain its small size. Concerning the squamous cell carcinoma in the Group 2 female #2542, Dr. Bolte affirms it was not seen macroscopically. He explains this as due to an endophylic rather than an exophylic growth patter, which would make it difficult to be seen macroscopically during necropsy. While Dr. Swenberg characterized the tumor as being large. Dr. Bolte here says it would need to be massive in size to be seen macroscopically in the routine procedure.

Concerning clarification of the historical control data for the CD rat as presented in his August 11 correspondence, Dr. Bolte confirms incidences of squamous cell carcinoma of the hard palate among females was 0/1691 and the incidence of papilloma of the lip among males was 0/1686.

The following attachments are not available electronically. Please see file copy.

MEMORANDUM:

013870

To: Auletta, Carol

From: Bolte, Henry

Date: April 19, 1999

Re: 90-3641A: A 24-Month Oral Toxicity/Oncogenicity Study of Malathion in the Rat via Dietary Administration; Response to a telefax from Meena Sonawane to Carol Auletta, April 14, 1999.

Why Dr. Bolte changed his diagnosis from the first study to the recent peer reviewed submission:

The request from the sponsor, directed by the EPA, to cut additional sections of nasoturbinal tissues from all rats on test resulted in an evaluation of the new sections and a re-evaluation of sections previously examined for the sake of consistency. As a result, some terminology, based on current knowledge, and a few findings in the original report were changed prior to submitting the results and report to Dr. Swenberg for peer review.

Were all sections recut?

Additional sections requested by the sponsor were cut for all animals on test. Sections which had been previously cut were NOT re-cut. However, as stated above, when the new sections of nasoturbinal tissues were evaluated, all of the previous sections of nasoturbinal tissues were re-evaluated for the sake of consistency. Sections from levels 2 and 4 of the nasoturbinal tissues were the same as those evaluated for the original report; No new sections from levels 2 and 4 were recut (the only exceptions would have been a recut of sections not originally considered to be suitable for evaluation).

Animal #5040, Group V, (high dose) male:

This animal still has a neoplasm involving the nasoturbinal tissues. When only sections from Levels 2 and 4 were available, a fragment of a neoplasm obviously originating from the respiratory epithelium, was seen in the nasal lumen. However, when additional sections were cut, this neoplasm was seen to be attached to the respiratory mucosa in level 1 and was identified to be an adenoma of respiratory epithelium. Dr Swenberg agreed with this at the time of the peer review and per the agreement of Drs Swenberg and Bolte, the fragments of this neoplasm in the lumen of levels 2 and 3 were described to be present in the nasal lumen. At the time of the original reading (prior to that for the peer review) this neoplasm was categorized as a carcinoma of respiratory epithelium, however, when the site of attachment was found, the neoplasm could be more appropriately evaluated and the diagnosis was changed to adenoma of respiratory epithelium;

Animal #5503 Group V (high dose) female:

During my original evaluation of level 4 of the nasoturbinal tissues from the animal, I concluded that a squamous cell carcinoma may have originated from a tooth alveolus. During the peer review with Dr. Swenberg, we discussed the origin of this neoplasm and jointly concluded that the site of origin was the palate adjacent to the tooth.

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Huntingdon
Life Sciences

MEMORANDUM:

TO:	AULETTA, CAROL S. (STUDY DIRECTOR)
FROM:	BOLTE, HENRY F. (STUDY PATHOLOGIST)
CC:	GOSSELIN, SYLVIE J.(VICE PRESIDENT OF RESEARCH)
DATE:	11, AUGUST, 1999
RE:	90-3641-A 24-MONTH ORAL TOXICITY/ONCOGENICITY STUDY OF MALATHION IN THE RAT VIA DIETARY ADMINISTRTION

After euthanasia of test animals for postmortem examination, all external surfaces, all cavities, including the oral cavity, the eyes and all extremities are examined for the presence of macroscopic abnormalities. The tissues associated with the oral cavity include the lips, gingiva, teeth, buccal mucosa, tongue and hard palate. Macroscopic findings are noted and sampled for microscopic examination. For studies which require the microscopic examination of nasoturbinal tissues, the portion of the skull containing the nasoturbinal tissue, and attached soft tissue (paranasal and portions of the buccal mucosa) and the teeth, gingiva and hard palate are again examined macroscopically at the time that the tissues are trimmed; macroscopic findings are noted and processed for microscopic examination.

Sections of the skull containing the nasoturbinal tissues also contain the following: bone, bone marrow, the olfactory bulb of the brain, hard palate, teeth, gingiva, nasolacrimal ducts, paranasal soft tissue, buccal mucosa and on occasion skin. In inhalation studies, all are examined microscopically; this group of tissues are rarely examined in non-inhalation studies. For an occasional chronic study, the tongue is a protocol required tissue which is examined microscopically.

Neoplasms involving the tissues lining the oral cavity or arising from the tooth alveolus are uncommon. In inhalation studies, where the nasoturbinal and associated tissues are examined. they occasionally occur as a solitary incidental finding. In chronic studies involving a large number of animals exposed to escalating dose levels of a test article a finding, even if rare, with an incidence of one should not be considered to be treatment related regardless of the dose level at which it occurred. Most findings, inorder to be considered treatment related, usually have incidences greater than one and with some semblance of a dose related pattern.

The historical control data base at Huntington Life Sciences/Princeton was reviewed for the presence of neoplasms of tissues associated with the oral cavity. Inhalation studies were selected since oral tissues are also examined with the nasoturbinal tissues. Four recent studies had 453 unexposed, control rats (227 males, 226 females). A squamous cell carcinoma arising from a tooth alveolus occurred in 1/227 males and a fibrosarcoma arising from periodontal tissue occurred in two rats, 1/227 males and 1/226 females.. The rare occurrence of squamous cell carcinomas and fibrosarcomas are usually sequellae to periodontal disease. Periodontal disease, uncommon in aging and aged rats, is characterized by the presence of impacted food particles, inflammation ranging from acute to chronic, fibrosis and hyperplasia of the squamous epithelium lining the tooth alveolus. The severity of periodontal disease is variable and on occasion it can be severe with extensive squamous cell hyperplasia.

Incidence of neoplasms of tissues associated with the oral cavity in untreated control rats have been reported for both the CD® and the Fisher 344 Rat [1,2] In the CD® rat, the incidence oral neoplasms in 3377 rats (1680 males, 1691 females) used in 26 long term studies initiated in December 1989 to April 1995 was as follows:

Squamous cell carcinoma-hard palate: 1/1686 males.
Squamous cell carcinoma-site not specified: 1/1686 males and 3/1691 females.
Papilloma: lip: 1/1691 females.

In the Fisher 344 rat, the incidence of oral neoplasm in 3919 untreated rats (1936 males, 1983 females) and in 3899 corn oil gavage treated rats (1949 males, 1950 females) was as follows:

UNTREATED RATS:

Squamous cell papilloma-site not specified: 1/1936 males, 1/1983 females.
Squamous cell carcinoma-site not specified: 1/1936 males, 1/1983 females.
Tooth-odontoma: 2/1936 males, 0/1983 females.

CORN OIL GAVAGE:

Squamous cell papilloma-site not specified: 6/1949 males, 6/1950 females.
Squamous cell carcinoma-site not specified: 0/1949 males, 0/1950 females.

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[1]Giknis, Mary L. A. and Clifford, Charles B.: Spontaneous neoplastic Lesions and Survival in Crl:CD® (SD)BR Rats Maintained on Dietary Restriction; Charles River Laboratories, 1998.
[2]Boorman, Gary A. *et al.*:: Tumor Incidences in Fischer 344 Rats: NTP Historical Data; Pathology of the Fischer Rat; pp-555-564; Academic Press, Inc., New York, New York, 1990.

013870

MEMORANDUM:

TO: AULETTA, CAROL S. (STUDY DIRECTOR)

FROM: BOLTE, HENRY F. (STUDY PATHOLOGIST)

CC: GOSSELIN, SYLVIE J.(VICE PRESIDENT OF RESEARCH)

DATE: 28, September, 1999

RE: 90-3641:-A 24-MONTH ORAL TOXICITY/ONCOGENICITY STUDY OF MALATHION IN THE RAT VIA DIETARY ADMINISTRTION: RESPONSE TO QUESTIONS SUBMITTED TO HENRY BOLTE, 23, SEPTEMBER, 1999.

1): Affirmation that the oral cavities (including tongue, mucosa, palate, gingiva, etc.) of all animals were examined macroscopically, and found to be negative consistent with laboratory records.

All tissue required per protocol were listed in the incidence summary of the macroscopic findings even if no macroscopic findings were noted. Non-protocol tissues were listed only if macroscopic findings were noted, even if only for one animal. Numerous tissues, including those associated with the oral cavity, not protocol required, were examined per Standard Operating Procedure (SOP); if there were no macroscopic findings, these tissues were not included in the incidence summary of macroscopic findings.

2a): Assurance that the adenoma seen in the tissues of the nasal cavity was not seen macroscopically.

Based on microscopic examination, the adenoma in the nasoturbinal tissues was very small. Due to its small size, it was unlikely that it would have been seen when examined macroscopically at the time that the nasoturbinal tissues were trimmed for processing toward microscopic evaluation.

2b): Assurance that the squamous cell carcinoma of the tooth alveolus was not seen macroscopically.

Squamous cell carcinomas arising from the tooth alveolus usually have an endophytic rather the exophytic growth pattern. Unless massive in size with considerable tissue disruption, which was not the case in this study, it is not likely to be seen macroscopically at the time of necropsy or at the time that the tissues are trimmed for processing toward microscopic evaluation.

3): Incidence of squamous cell carcinoma of the hard palate in females and papilloma of the lip in males:

The assumption that the incidence of squamous cell carcinoma of the hard palate among females was 0/1691 and that the incidence of papilloma of the lip among males was 0/1686 is correct.

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FROM MRID: 43942901

*** PATH/TOX SYSTEM OUTPUT ***
A 24-MONTH ORAL TOXICITY/ONCOGENICITY STUDY
OF MALATHION IN THE RAT VIA DIETARY ADMINISTRATION
INDIVIDUAL ANIMAL DATA SHEET

STUDY NUMBER: S03641

ANIMAL NUMBER: 5040 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (D)
DATE OF DEATH: 07/31/94 STUDY DAY OF DEATH: 579 STUDY WEEK OF DEATH: 83 TERMINAL BODY WEIGHT: 187.3 GRAMS

*** PATHOLOGY OBSERVATIONS (CONTINUED) ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
LIVER		
	MICRO: -SLIGHT	-CONGESTION
	-MINIMAL	-PERIVASCULAR/PERIDUCTAL LYMPHOID CELLS
	-MINIMAL	-HEPATOCELLULAR CYTOPLASM: VESICULATED/VACUOLATED
	-MINIMAL, MULTI-FOCAL	-CHOLANGIOFIBROSIS
LUNGS		
	MICRO: -SLIGHT	-CONGESTION
	-MODERATE, MULTI-FOCAL	-VESSEL: THROMBUS
	-MINIMAL, MULTI-FOCAL	-VESSEL(S): MINERAL DEPOSIT(S)
	-SLIGHT	-PERIVASCULAR/PERIBRONCHIOLAR LYMPHOID CELLS
	-SLIGHT, MULTI-FOCAL	-GRANULOMATOUS INFLAMMATION/GRANULOMA(S)
	-SLIGHT, MULTI-FOCAL	-ALVEOLAR WALLS: DISRUPTED
	-SLIGHT	-ALVEOLAR/INTRAALVEOLAR MACROPHAGES
LYMPH NODE		
	MICRO: -SLIGHT	-CONGESTION
	-MODERATE	-SINUS ECTASIA
	HISTOPATHOLOGICAL COMMENT:	>PRESENTED WITH SALIVARY TISSUE
MAMMARY		
	MICRO: -TISSUE MISSING	
MEDIASTINAL LN		
	MICRO: -TISSUE MISSING	
MESENTERIC LN		
	MICRO: -MODERATE	-SINUS ECTASIA/CYSTIC DILATION
	-MODERATE	-RETICULOENDOTHELIAL CELLS: BROWN PIGMENT
	-MODERATE	-RETICULOENDOTHELIAL CELL HYPERPLASIA
	-MODERATE	-LYMPHOID CELL DEPLETION/ATROPHY
NOSE/TURB SEC 2		
	MICRO: -SLIGHT	-NASAL LUMEN: EOSINOPHILIC MATERIAL
	-MODERATE	-NASAL LUMEN: INFLAMMATORY CELLS/CELL DEBRIS/ METACHROMATIC-BASOPHILIC AMORPHOUS MATERIAL
	-MARKED	-NASAL MUCOSA (RESPIRATORY): CONGESTION
	-SLIGHT, MULTI-FOCAL	-NASAL MUCOSA (RESPIRATORY): HYPERPLASIA
	-MODERATE	-NASAL MUCOSA (OLFACTORY): CONGESTION
	-MARKED	-NASAL MUCOSA (OLFACTORY): EPITHELIUM-DEGENERATION
	-MARKED	-NASAL MUCOSA (OLFACTORY): OLFACTORY EPITHELIUM REPLACED BY CILIATED AND NONCILIATED COLUMNAR EPITHELIAL CELLS
	-MINIMAL	-VOMORONASAL ORGAN: EOSINOPHILIC MATERIAL
	-SLIGHT	-NASOLACRIMAL DUCT(S): EOSINOPHILIC MATERIAL
	-MINIMAL	-NASOLACRIMAL DUCT(S): INFLAMMATORY CELLS/CELL DEBRIS
	-NEOPLASM PRESENT	-M- NASAL MUCOSA (OLFACTORY): CARCINOMA

SLIDE REVIEW WORK SHEET FROM MRID: 44782301

Chemical Name: MALATHION Chemical Number:

Laboratory: PHARMACO::LSR Client Project Id.: 903641A Sacrifice: 24-MONTH

Group Id: 5 Dose: Sex & Species: MALE RAT

Animal Id.	Histology Number	No. of Slides	Study Pathologist's Diagnosis	Reviewing Pathologist's Comments	Comments	Action To Be Taken
5040	Cont'd		NOSE/TURB SEC 2 - NASAL MUCOSA (RESPIRATORY): SUBACUTE (CHRONIC ACTIVE)/CHRONIC INFLAMMATION, SLIGHT	AGREE		
			NOSE/TURB SEC 2 - NASAL MUCOSA (RESPIRATORY): EPITHELIUM-HYPERPLASIA, MULTI-FOCAL, SLIGHT	AGREE		
				NOSE/TURB SEC 2 - ADENOMA (51)	AGREE WITH REVIEWING PATHOLOGIST BUT CHANGE TO NASAL LUMEN EXTENDING FROM NOSE/TURB SEC 1	DATA BASE CHANGE: ADD DIAGNOSIS AS NOTED BY STUDY PATHOLOGIST'S COMMENT; AGREEMENT BY REVIEWING PATHOLOGIST
			NOSE/TURB SEC 2 - NASAL MUCOSA (OLFACTORY): CONGESTION, MODERATE	AGREE		
			NOSE/TURB SEC 2 - NASAL MUCOSA (OLFACTORY): EDEMA, SLIGHT	AGREE		
			NOSE/TURB SEC 2 - NASAL MUCOSA (OLFACTORY): EPITHELIUM-DEGENERATION/ATROPHY, MARKED	AGREE		
			NOSE/TURB SEC 2 - NASAL MUCOSA (OLFACTORY): OLFACTORY EPITHELIUM REPLACED BY CILIATED AND NONCILIATED COLUMNAR EPITHELIAL CELLS, MARKED	AGREE		
			NOSE/TURB SEC 2 - VOMORONASAL ORGAN: EOSINOPHILIC MATERIAL, MINIMAL	AGREE		
			NOSE/TURB SEC 2 - NASOLACRIMAL DUCT(S): EOSINOPHILIC AND/OR GOLDEN BROWN MATERIAL, SLIGHT	AGREE		

FROM: MRID 43942901

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*** PATH/TOX SYSTEM OUTPUT ***
A 24-MONTH ORAL TOXICITY/ONCOGENICITY STUDY
OF MALATHION IN THE RAT VIA DIETARY ADMINISTRATION
INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 20-FEB-96
PAGE: 2442

STUDY NUMBER: 903641

ANIMAL NUMBER: 5503 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 01/03/95 STUDY DAY OF DEATH: 735 STUDY WEEK OF DEATH: 105 TERMINAL BODY WEIGHT: 196.5 GRAMS

* * * PATHOLOGY OBSERVATIONS (CONTINUED) * * *

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
MEDIASTINAL LN		
	MICRO: -SLIGHT	-PLASMA CELL HYPERPLASIA
MESENTERIC LN		
	MICRO: -MODERATE	-SINUS ECTASIA/CYSTIC DILATION
	-SLIGHT	-SINUSES: FREE ERYTHROCYTES
	-SLIGHT	-RETICULOENDOTHELIAL CELLS: ERYTHROPHAGIA
	-MODERATE	-RETICULOENDOTHELIAL CELLS: BROWN PIGMENT
	-SLIGHT	-RETICULOENDOTHELIAL CELL HYPERPLASIA
	-SLIGHT	-PLASMA CELL HYPERPLASIA
	HISTOPATHOLOGICAL COMMENT:	>FINDINGS NOTED INCLUDE THOSE SEEN IN LYMPH NODES PRESENTED WITH THE PANCREAS
NOSE/TURB SEC 2		
	MICRO: -SLIGHT	-NASAL MUCOSA (RESPIRATORY): GLANDS DILATED
	-SLIGHT, MULTI-FOCAL	-NASAL MUCOSA (RESPIRATORY): HYPERPLASIA
	-SLIGHT	-NASAL MUCOSA (OLFACTORY): GLANDS DILATED
	-SLIGHT, MULTI-FOCAL	-NASAL MUCOSA (OLFACTORY): EPITHELIUM-DEGENERATION
	-MINIMAL, FOCAL	-NASAL MUCOSA (OLFACTORY): EPITHELIUM-CYSTS
	-SLIGHT	-NASAL MUCOSA (OLFACTORY): SUBACUTE (CHRONIC ACTIVE)/ CHRONIC INFLAMMATION
	-SLIGHT	-NASOLACRIMAL DUCT(S): EOSINOPHILIC MATERIAL
	-MINIMAL	-NASOLACRIMAL DUCT(S): MUCOSA- SUBACUTE (CHRONIC ACTIVE)/CHRONIC INFLAMMATION
NOSE/TURB SEC 4		
	MICRO: -MODERATE	-NASAL LUMEN: EOSINOPHILIC MATERIAL
	-SLIGHT	-NASAL LUMEN: INFLAMMATORY CELLS/CELL DEBRIS/ METACHROMATIC-BASOPHILIC AMORPHOUS MATERIAL
	-MINIMAL, MULTI-FOCAL	-NASAL MUCOSA (RESPIRATORY): BASOPHILIC MATERIAL
	-SLIGHT, MULTI-FOCAL	-NASAL MUCOSA (OLFACTORY): BASOPHILIC MATERIAL
	-MODERATE, MULTI-FOCAL	-NASAL MUCOSA (OLFACTORY): EPITHELIUM-DEGENERATION
	-MODERATE, MULTI-FOCAL	-NASAL MUCOSA (OLFACTORY): EPITHELIUM-HYPERPLASIA
	-MODERATE, MULTI-FOCAL	-NASAL MUOCSA (OLFACTORY): EPITHELIUM-CYSTS
	-MODERATE	-PERIODONTAL DISEASE (CHARACTERIZED BY ONE OR MORE OF THE FOLLOWING; FOREIGN MATERIAL IMPACTED AROUND THE TOOTH AND IN THE ALVEOLUS, EROSIONS/ULCERS, ACUTE-CHRONIC INFLAMMATION, FIBROSIS, SQUAMOUS CELL HYPERPLASIA AND/OR OSTEOLYSIS OF THE THE ADJACENT BONE)
	-NEOPLASM PRESENT	-M- SQUAMOUS CELL CARCINOMA ARISING FROM THE SQUAMOUS EPITHELIUM LINING THE ALVEOLUS OF A TOOTH
OPTIC NERVE		
	MICRO: -PRESENT	-STAIN: HEMATOXYLIN/EOSIN
	-PRESENT	-STAIN: LUXOL FAST BLUE

5062

013870

FROM MRID 44782301

14

SLIDE REVIEW WORK SHEET

Chemical Name MALATHION

Chemical Number

Laboratory PHARMACO::LSR

Client Project Id. 903641A

Sacrifice 24-MONTH

Group Id 5

Dose

Sex & Species FEMALE RAT

Animal Id.	Histology Number	No. of Slides	Study Pathologist's Diagnosis	Reviewing Pathologist's Comments	Comments	Action To Be Taken
5503	Cont'd		NOSE/TURB SEC 4 - M- PALATE: SQUAMOUS CELL CARCINOMA,-NEOPLASM PRESENT	AGREE		
			NOSE/TURB SEC 5 - NASOLACRIMAL DUCT(S): EOSINOPHILIC/BROWN MATERIAL, MINIMAL	AGREE		
5504		5	NOSE/TURB SEC 1 - NASAL LUMEN: INFLAMMATORY CELLS/CELL DEBRIS/ METACHROMATIC AMORPHOUS MATERIAL, SLIGHT	AGREE		
			NOSE/TURB SEC 1 - NASAL MUCOSA (RESPIRATORY): GOBLET CELL HYPERTROPHY/HYPERPLASIA, MINIMAL	AGREE		
			NOSE/TURB SEC 1 - NASAL MUCOSA (RESPIRATORY): GLANDS DILATED, MULTI- FOCAL, SLIGHT	AGREE		
			NOSE/TURB SEC 1 - NASAL MUCOSA (RESPIRATORY): SUBACUTE (CHRONIC ACTIVE)/ CHRONIC INFLAMMATION, MULTI-FOCAL, SLIGHT	AGREE		
			NOSE/TURB SEC 1 - VOMORONASAL ORGAN: EOSINOPHILIC MATERIAL, MINIMAL	AGREE		
			NOSE/TURB SEC 1 - VOMORONASAL REGION: GLANDS DILATED, SLIGHT	AGREE		
			NOSE/TURB SEC 1 - NASOLACRIMAL DUCT(S): EOSINOPHILIC/BROWN MATERIAL, MODERATE	AGREE		
			NOSE/TURB SEC 1 - NASOLACRIMAL DUCT(S): INFLAMMATORY CELLS/DESQUAMATED EPITHELIAL CELLS/CELL DEBRIS, MODERATE	AGREE		