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To: <coshita@oehha.ca.gov>
Date: 5/5/2009 11:37 AM
Subject: Benoxacor: Response to Prioritization of Chemicals for Consultation by the CIC
Attachments: Benoxacor_SyngentaResponse_Prioritization_CIC_consult 5-5-09.pdf

Dear Ms. Oshita,

Attached please find a document containing comments from Syngenta Crop Protection, Inc regarding the potential selection for evaluation by the CIC of benoxacor. The document outlines the reasons why Syngenta believes that benoxacor does not meet the necessary selection criteria.

We appreciate the opportunity to provide these comments and we are willing to discuss any questions you may have. Please contact me via e-mail or at the numbers below.

Regards,

Debbie Stubbs | Senior Regulatory Manager | State Affairs Dept. |
Syngenta Crop Protection | P.O. Box 18300 | Greensboro, NC 27419

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Benoxacor

Syngenta Response to OEHHA's Proposed Inclusion of Benoxacor on the Prioritization of Chemicals for Carcinogen Identification Committee Review (March 2009)

Response

DATA REQUIREMENT(S):	Not Applicable
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COMPLETION DATE:	May 5, 2009
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STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

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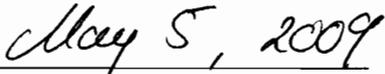
GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The assessment contained in this volume was not conducted in accordance with EPA Good Laboratory Practices, 40 CFR Part 160.

Study Director: There is no GLP study director for this volume.



Ursula May-Hertl, Ph.D.
Author



Date ✓

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1.0 INTRODUCTION

The office of Environmental Health Hazard Assessment (OEHHA) is proposing 38 chemicals for review by the Carcinogen Identification Committee (CIC) under Proposition 65, including Benoxacor (4-(dichloroacetyl)-3,4-dihydro-3methyl-2H-1,4benzoxazine). In this document, Syngenta requests OEHHA to reconsider the necessity to review benoxacor for consideration as a human carcinogen based on its proposed mode of action, which indicate that the rodent tumors would not be relevant to humans.

Benoxacor is used as a safener in certain S-metolachlor and metolachlor herbicide formulations and is included in seven formulations that are registered in California. The purpose of benoxacor in these formulations is to provide added safety to the application of the product to corn. Therefore the primary use of the benoxacor containing products is in the major corn growing states in the mid-west. Hence the exposure potential in California from benoxacor is extremely low due to the limited number of uses and applications per year expected in California.

OEHHA included benoxacor on the CIC list due to the presence of forestomach tumors findings in the rodent studies that were observed at the highest dose rates. There are no human epidemiological studies suggesting evidence of carcinogenicity for benoxacor.

Consistent with the USEPA Health Effects Division (HED) Carcinogenicity Peer Review Committee, Syngenta concluded that the rodent forestomach tumors in the benoxacor studies are caused by a non-genotoxic mechanism of action (i.e. cell proliferation induced by forestomach epithelial irritation caused by prolonged exposure) and are not relevant to humans. US EPA's HED Carcinogenicity Peer Review Committee concluded, that based on the weight of evidence, the use of MOE methodology to estimate human risk should be used and agrees, that the forestomach tumors have little or no relevance to humans (US EPA 1997).

In this document, Syngenta requests OEHHA to reconsider the need to review benoxacor based on its proposed mode of action, which indicate that the rodent tumors would not be relevant to humans.

2.0 REGISTERED BENOXACOR CONTAINING PRODUCTS IN CALIFORNIA

Benoxacor is an herbicide safener formulated in certain S-metolachlor and metolachlor containing products to protect corn seedlings from damage. The eight products registered in California are listed below.

Table 1 Benoxacor Containing Products Registered in California

Product Name	EPA Reg. No.	Registrant
Bicep II Magnum®	100-817	Syngenta Crop Protection
Dual II Magnum®	100-818	Syngenta Crop Protection
Medal® II Herbicide	100-965	Syngenta Crop Protection
Medal® II AT Herbicide	100-1165	Syngenta Crop Protection
Brawl II ATZ Herbicide	100-817-55467	Tenkoz Inc
Brawl II Herbicide	100-818-55467	Tenkoz Inc
Agrisolutions Charger Basic	1381-207	Winfield Solutions LLC
Parallel Herbicide	66222-87	Makhteshim-Agan of North America

The maximum concentration of benoxacor present in any of the herbicide formulations is 4.25% (w/w). These products are applied pre-emerge or early post-emergence at a typical use rate of the active ingredient (AI) of 1.33 pts/acre (1.27 lbs AI/acre). This typical AI rate would correspond to 0.06 lbs of benoxacor/acre. Although the label directions for these products indicate the range of crops include corn, cotton, peanuts, pod crops, potatoes, safflowers, grain or forage sorghum, and soybeans, the primary use and benefit would be for corn.

3.0 CRITERIA TO IDENTIFY BENOXACOR FOR REVIEW BY THE CIC UNDER PROPOSITION 65

In responding to the OEHHA’s proposing of benoxacor for review by the CIC under proposition 65, the first step was taken to determine if the criteria for proposing benoxacor are met. The second step was to review the weight of evidence of all relevant benoxacor data.

According to the “Prioritization of Chemicals for Carcinogen Identification Committee Review: Proposed Chemicals for Committee Consideration and Consultation March 2009” document, the hazard was assessed by application of an epidemiologic data screen and an animal data screen. Chemicals with findings from either of these hazard screens were then subjected to a preliminary toxicological evaluation, which considered additional information relevant to carcinogenicity, such as genotoxicity studies, mode of action, metabolism and pharmacokinetics. If the overall weight of evidence indicates a possible concern for carcinogenicity, the chemicals are proposed for possible preparation of hazard identification materials.

The OEHHA document contains a table of the chemicals selected for CIC consultation, detailing the exposure characteristics and types of studies that provide evidence of carcinogenicity. In this table benoxacor is listed as resulting in widespread exposure and having two or more animal studies showing carcinogenicity. No further relevant data are listed.

3.1 Widespread Exposure

Benoxacor is used as an herbicide safener in S-metolachlor and metolachlor formulations. The maximum concentration of benoxacor present in any of the eight herbicide products registered in California is 4.25 % (w/w) benoxacor. Of the Syngenta registered products (see Table 1), our records indicate that there were no sales of Bicep II Magnum®, Medal® II AT or Medal® II in California over the last three (2006 – 2008) years. The average sales volume of the last three years (2006 to 2008) for Dual II Magnum® was 454 gallons per year. At a typical use rate of 1.33 pts/acre, this amounts to 4,468 pounds active ingredient, which would treat about 2,752 acres. We believe that sales of the Tenkoz products, which are supplemental distributor registrations for Syngenta products, would be less than those for the Syngenta products. The Winfield Solutions product was registered in July 2007 and Makhteshim-Agan product was just registered in January 2008. We believe both of these products would have had limited, if any sales since their registrations.

Based on these estimates, benoxacor is only used on 0.011% of the total farmed land in California (USDA National Agricultural Statistics Service) or 0.0027% of the total land of California (US Geological Survey). Benoxacor was not detected in any food commodities (LOQ of 0.005 ppm) and the actual use volume in California is marginal. According to the label directions, Dual II Magnum® is registered for weed control in corn, cotton, peanuts, pod crops, potatoes, safflowers, grain or forage sorghum, and soybeans. Contrary to the statement in the appendix for benoxacor, there is no use on greenhouse flowers. Based on the limited use pattern of benoxacor, Syngenta requests OEHHA to reconsider benoxacor's categorization to result in widespread use and exposure.

3.2 Relevant Studies

There are no human epidemiological studies suggesting evidence of carcinogenicity for benoxacor.

The animal carcinogenicity data for benoxacor that were listed in the appendix of the OEHHA document include the two year rat study (Ryle 1993a), the 80 week mouse study (Ryle 1993b), and genotoxicity studies that were referred from the USEPA HED Carcinogenicity Peer Review of Benoxacor document (US EPA 1997). Furthermore, an IARC document (IARC 2003) was referenced regarding the predictive value of rodent forestomach and gastric neuroendocrine tumors in evaluating the carcinogenic risks to humans.

3.2.1 Toxicity Studies

Benoxacor did not show any mutagenic activity *in vitro* or *in vivo* in a series of genotoxicity studies (US EPA 1997). It did not show any mutagenic activity in two Salmonella/mammalian-microsome mutagenicity tests with or without metabolic activation (CIBA GEIGY Ltd 1988a and 1988b), and no unscheduled DNA synthesis occurred in three autoradiographic DNA-repair tests on rat hepatocytes and human fibroblasts (CIBA GEIGY

Ltd 1986a, 1987a, and 1987b). No evidence of mutagenicity was observed in a micronucleus test (Chinese Hamster) (CIBA GEIGY Ltd 1986b).

In the oncogenicity studies, benoxacor caused forestomach tumors in male and female mice and rats at the top dose levels. The tumors were accompanied by hyperplastic changes of the forestomach epithelium (papillomateous hyperplasia and/or epithelial hyperplasia/hyperkeratosis in rats and papillomatous hyperplasia in mice at the two highest dose levels). In both species the tumor induction occurred only after prolonged administration (>52 weeks) and there was a long latency period for the occurrence of malignant tumors (>52 weeks). No significant pre-neoplastic or neoplastic lesions were observed in any other organs. For further information, please review the study summaries in section 6 and the USEPA HED CARC (1997).

3.2.2 Relevance of Rodent Forestomach Tumors for Human Cancer Risk Assessment

Evidence exists for both genotoxic and non-genotoxic mechanisms of action for chemical substances that induce forestomach tumors. Genotoxic agents induce tumors by interacting with DNA and causing irreversible genetic alterations, and the genotoxic mechanisms of action of forestomach tumors are considered to be relevant human carcinogens. However, there are non-genotoxic mechanisms of compounds that cause forestomach tumors which are considered not relevant to humans. For example, in the case of chemicals that act through non-mutagenic mechanisms and cause tumors only in the forestomach, chronic inflammation or local irritation of forestomach mucosa may lead to continuous induction of cell proliferation, hyperplasia, and ultimately carcinomas. These chemicals have typically not been considered to be relevant for human carcinogenicity (IARC 2003, Procter *et al.* 2007). In assessing the relevance of rodent forestomach tumor studies to human cancer risk assessment, the following issues should be considered: the method of administration and dose level, the specificity of the carcinogen to the forestomach, the applicability of the forestomach to human organs, and the mode of action for tumor formation (Procter *et al.* 2007).

Regarding the applicability of the rodent forestomach to humans, the digestive system of rats and mice is anatomically different from humans. The rodent stomach consists of a non-glandular forestomach region (about 3/5 of the stomach volume) and a glandular stomach region. The two regions of the stomach are separated by an elevated fold, the limiting ridge, and the mucosa of the forestomach is lined with a keratinized, stratified squamous epithelium. Humans do not have a functional analogue to the forestomach, but the human esophagus and the oral cavity do have comparable squamous epithelial tissue. Functionally, however, there are significant differences in terms of tissue exposure. The exposure duration of a chemical to the epithelial tissue in the oral cavity and the esophagus of humans is much shorter and the concentration of the chemical in these organs is lower than in the rodent forestomach. This is due to the fact that the forestomach serves as a food reservoir which leads to prolonged exposure of the epithelial tissue to ingested chemicals.

A total of 120 substances have been identified to cause tumors in the forestomach of rodent species (Dybing and Sanner 2003). Among those, 84% caused also tumors at other sites. Almost all of the forestomach carcinogens show positive responses to the Salmonella

mutagenicity test or show a positive genotoxic response in at least one other test system. This strongly suggests a genotoxic mechanism of the forestomach tumor induction for those substances.

In contrast, Benoxacor is not genotoxic in the battery of genotoxicity studies, and the results of the rat and mouse oncogenicity studies with benoxacor indicate benoxacor does not significantly increase tumors at other sites other than the forestomach. Furthermore, no hyperplastic or neoplastic responses were observed in a chronic dog study (Wood, 1992). Benoxacor was administered by capsule to Beagle dogs at dose rates up to 80 mg/kg/day, which is similar to the maximum dose rate used in the rat study (59 mg/kg/day). No macroscopic or microscopic effects on the stomach tissue of the dogs were observed; the stomach of the dog is far more similar to humans. Together with the fact that benoxacor did not show any mutagenic response this is an important indication that the forestomach tumors observed in the rodent studies with benoxacor are most likely not caused by a genotoxic mechanism.

The forestomach tumors in rodents were accompanied by hyperplasia and/or hyperkeratosis of the forestomach epithelium, indicating a progression of hyperplastic to neoplastic lesions. A similar mechanism of action has been established for butylated hydroxyanisole (Williams and Iatropulus 2003), where the authors indicated that chronically sustained hyperplasia can be a major determining factor for the development of forestomach neoplasias. In the chronic studies with benoxacor, no significant increase in forestomach tumors was observed at doses where no induction of cell proliferation occurred. Both effects only occurred together at the top doses. It is likely that the tumor response in the chronic studies in rats and mice is dependent on a continuous exposure to benoxacor for a long duration and at relatively high levels.

3.2.3 US EPA Carcinogenicity Peer Review of Benoxacor

In 1997, the Health Effects Division (HED) Carcinogenicity Peer Review Committee (CPRC) (USEPA 1997) evaluated the weight-of-evidence on benoxacor in regard to its carcinogenic potential. The following toxicological data were considered for the weight-of-evidence consideration: the results from the mouse and rat chronic studies, the results from the supplement to the subchronic rat study (Thakur 1996), mechanistic data on the forestomach tumor induction provided by Syngenta (not considered to be conclusive) and the results of the genotoxicity studies. Based on the toxicological profile, the CPRC recommended the use of Margin of Exposure (MOE) methodology, rather than Q*, to estimate the human risk for benoxacor. (The NOEL from the rat study of 20.6 mg/kg/day was selected to be used in the MOE carcinogenicity risk assessment). The consensus of the CPRC was that benoxacor was characterized in terms of its carcinogenic potential as “cannot be determined, but suggestive”, based on increases in forestomach tumors in both sexes in mice and rats and it was concluded that the forestomach tumors have little or no relevance to humans.

4.0 DISCUSSION

Benoxacor has a robust toxicological database that has been thoroughly reviewed by the USEPA prior to registration. Benoxacor is not genotoxic, however an increased incidence of forestomach tumors was observed at the highest dose levels in the rat and mouse carcinogenicity studies. There was no increased incidence of tumors at any other site. The forestomach tumors were accompanied by hyperplasia and/or hyperkeratosis of the forestomach epithelium, indicating a progression of hyperplastic to neoplastic lesions similar to what was observed with other non-genotoxic forestomach carcinogens. These compounds cause forestomach tumors by the sustained proliferation of the forestomach epithelium due to their irritancy or cytotoxicity.

However, it is largely understood that the non-genotoxic mechanism of rodent forestomach tumors is considered not relevant to man for a number of reasons, primarily due to the histological and functional differences between the human and rodent stomach. Rodent stomachs are divided into a forestomach, which serves as a food reservoir, and a glandular stomach. Humans do not possess a forestomach. The prolonged exposure of the forestomach epithelium to the irritant and/or cytotoxic chemical is believed to be the main factor for the increased epithelial proliferation and the subsequent tumor formation. Finally, an epithelium comparable to the forestomach epithelium in rodents is found in the oral cavity and oesophagus of man. However, even in rats and mice which developed forestomach tumors, no tumors or hyperplastic lesions were observed in the oesophagus. Furthermore, in a 52 week chronic feeding study with Beagle dogs at comparable dose rates, no hyperplastic or neoplastic lesions were observed.

Based on the MOA, mechanism of benoxacor, forestomach tumors should be considered not relevant to humans (no forestomach) or of limited relevance due to likely threshold nature of this mechanism of tumor induction (i.e., non-irritant or non-cytotoxic dose levels do not cause increase in tumors).

5.0 CONCLUSIONS

On the basis of the presented data, it is concluded that the forestomach tumors observed in the chronic mouse and rat studies are most likely not relevant to human cancer risk assessment. In addition, it is disputed that benoxacor meets the criteria of widespread exposure. Syngenta therefore requests that OEHHA to reconsider and remove Benoxacor from the listing for consideration as a human carcinogen.

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APPENDICES SECTION

Appendix 1 Toxicity studies with Benoxacor

Chronic Toxicity/Carcinogenicity Studies with Benoxacor

Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice (Ryle P. R. 1993)

CD-1 mice were fed benoxacor (50/sex/group) at dietary levels of 0, 10, 30, 600, and 1,200 ppm (0, 1.2, 3.7, 75, and 167 mg/kg/day for males and 0, 1.6, 4.7, 93, and 201 mg/kg/day for females) for 18 months. There was evidence of carcinogenicity at the two highest doses tested. Statistically ($p < 0.05$) significant increases of squamous cell papillomas and combined papillomas/carcinomas were seen in the nonglandular stomach (forestomach) in both sexes at the highest dose tested. There were also statistically significant positive trends for carcinomas in male mice and for papillomas and combined papilloma/ carcinoma in both sexes. The non-neoplastic lesions included increased forestomach excrescences and thickening of limiting ridge in males and females, papillomatous hyperplasia of the forestomach and epithelial hyperplasia of the forestomach in males, increased liver weight in males and females, as well as increased spleen hemo-siderosis, hemorrhagic ovarian cysts and parenchymal inflammatory hepatic cells in females.

For chronic toxicity, the NOEL was 30 ppm (3.7 mg/kg/day and 4.7 mg/kg/day in males and females, respectively) and the systemic LOEL was 600 ppm (75 mg/kg/day and 93 mg/kg/day in males and females, respectively) based on increased liver/body weight ratios in both sexes. The NOEL for mouse forestomach tumors was 3.7 mg/kg/day in males and 4.7 mg/kg/day in females with tumors occurring at 75 and 93 mg/kg/day in males and females. Dosing was considered adequate to assess the carcinogenic potential of benoxacor based on body weight reduction in males, treatment-related increased liver/body weight ratios in both sexes, and other treatment-related increased incidences of tumor and nontumor findings in the forestomach.

CGA154281: Combined Toxicity/Oncogenicity Study in Rats. Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats (Ryle P. R. 1993)

In a combined chronic toxicity/oncogenicity study, CrI:CD BR rats (70 /sex/group) were fed benoxacor dosed at dietary levels of 0, 10, 50, 500, and 1,000 ppm (0, 0.4, 2.0, 20.6, and 41 mg/kg/day for males and 0, 0.6, 2.8, 28.2, and 59 mg/kg/day for females) for two years. There was evidence of carcinogenicity at the highest dose tested. Statistically significant ($p < 0.01$) increasing trends were seen in male rats for forestomach squamous cell papillomas and papillomas and/or carcinomas combined. There was also a statistically significant ($p < 0.05$) increasing trend for forestomach squamous cell carcinomas in male rats. There were significant differences in the pair-wise comparisons of the male high-dose group with the controls for forestomach squamous cell papillomas ($p < 0.05$) and for papillomas and/or carcinomas combined ($p < 0.01$). Statistically significant ($p < 0.01$) increasing trends, and differences in the pair wise comparisons of the high-dose group with the controls, were seen in female rats for forestomach squamous cell papillomas and papillomas and/or carcinomas combined.

The non-neoplastic lesions included increased incidences of excrescence in the forestomach and raised areas of the epithelial aspects of the forestomach in males and females, epithelial hyperplasia and hyperkeratosis of the non-glandular stomach (forestomach) and papillomatous hyperplasia at the limiting ridge of the stomach in males and females, as well as liver and renal effects. The forestomach tumor incidences were above the historical control ranges in both sexes.

For chronic toxicity, the NOEL is 10 ppm (0.4 mg/kg/day and 0.6 mg/kg/day in males and females, respectively) and the systemic LOEL is 50 ppm (2.0 mg/kg/day in males) based on centrolobular hepatic enlargements with or without hepatocytic vacuolation in male rat livers. At a dose level of 2.6 mg/kg/day, hyperkeratosis of the forestomach in females was observed. The NOEL for rat forestomach tumors was 20.6 mg/kg/day in males and 28.2 in females with tumors occurring at 41 and 59 mg/kg/day in males and females.

52-week Oral (Capsule) Toxicity Study in the Beagle (Wood J.D. 1992)

Benoxacor was administered orally to male and female Beagle dogs at doses of 0, 1, 5, 40 and 80 mg/kg/day for 52 weeks. There was no evidence of carcinogenicity at any dose.

The NOEL was 5 mg/kg/day and the LOEL was 40 mg/kg/day based upon decreases in mean body weight gain in males and increases in adjusted liver and kidney weights and increased lipofuscin deposition in the kidney in both sexes.

Mutagenicity Studies with Benoxacor

Ames Test: CGA-54281 Technical: Salmonella/Mammalian-Microsome Mutagenicity Test

Non-mutagenic to TA98, TA1537 and TA1538 strains of *Salmonella typhimurium* with or without metabolic activation.

Concentrations tested: 1000, 2000, 3000, and 4000 µg/plate in first test; 250, 500, 1000, 2000, 3000, and 4000 µg /plate in second test. CIBA-GEIGY Ltd. (1988a)

CGA-154281 Technical: Salmonella/Mammalian-Microsome Mutagenicity Test

Non-mutagenic to TA98, TA1537 and TA1538 strains of *Salmonella typhimurium* with or without metabolic activation. Concentrations tested: 1000, 2000, 3000, 4000, 5000 and 8000 µg /plate in first test; 250, 500, 1000, 2000, 3000, and 4000 g/plate in second test. CIBA-GEIGY Ltd. (1988b)

Unscheduled DNA Synthesis:

CGA154281: Autoradiographic DNA Repair Test on Human Fibroblasts

Did not cause DNA damage or induce repair in a human fibroblast UDS assay without metabolic activation.

Concentration tested: 0.25, 1.25, 6.25, and 31.25 µg /m1 CIBA GEIGY Ltd. (1986a)

CGA-I54281 Technical: Autoradiographic DNA-Repair Test on Rat Hepatocytes

Did not cause DNA damage or induce repair in a rat hepatocyte UDS assay.

Dose levels tested: 0.1, 0.5, 2, 4, 6, 8, 10 and 20 4 µg/m1. CIBA GEIGY Ltd. (1987a)

CGA-154281 Technical: Autoradiographic DNA-Repair Test on Rat Hepatocytes

Did not cause DNA damage or induce repair in a rat hepatocyte UDS assay.

Concentration tested: 0.008, 0.04, 0.2, 1, 5, 10, 15, and 20 µg /m1 in the first trial; 0.0004, 0.002, 0.008, 0.04, 0.2, 1, 5, and 10 4 µg/m1 in the first trial. CIBA GEIGY Ltd. (1987b)

Micronucleus Assay:

CGA154281 Technical: Micronucleus Test (Chinese Hamster)

Negative. Under the conditions of the study, no evidence of mutagenic effects was observed in Chinese hamsters treated with Benoxacor Tech. There were no statistically significant increases in the number of micronucleated polychromatic erythrocytes as compared to the negative control animals; no clastogenic or aneugenic activity was reported. Doses ranged from 1250 to 5000 mg/kg. CIBA GEIGY Ltd. (1986b)

Other Relevant Studies

Subchronic Toxicity Study with CGA154281 Technical in Rats, (Osheroff, et al, 1986)

A subchronic feeding study in rats (15 rats/sex/group) dosed at 0, 10, 100, 300, 1000 and 6000 ppm (0, 0.5, 5.0, 15.0, 50 and 300 mg/kg/day) with Benoxacor for 92-93 days.

Supplement to Subchronic Toxicity Study in Rats (Thakur A.K 1996)

This study is the second histological re-evaluation of the forestomach tissues from the subchronic study in rats above. Based on the re-evaluation and statistical analysis of the incidence of pre-neoplastic lesions by the registrant, the increased incidence of nonglandular stomach hyperplasia noted in the 6000 ppm males and females is considered to be related to treatment. The hyperplasia of the limiting ridge region is generally considered as part of the overall changes that occurred within the nonglandular stomach. The statistically significant increased severity (Grade 2) of inflammation of the limiting ridge in the 1000 ppm females is considered biological variation and is not likely due to treatment.