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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Response to BASF comments on the DER (Doc. No. 00722) for the One-year Dog Study (408595-01) on Vinclozolin.

Tox. Chem. No.: 323C.
Project No.: 9-1610.
Record No.: 246455.

To: S Lewis, PM 21
Registration Division (H7505C)

From: David G Anderson, PhD. David G Anderson 10/23/89
Section 2, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Thru: Marion Copley, DVM
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and

Karl P. Baetcke 11/7/89

Karl P Baetcke, PhD
Chief Toxicology Branch 1 (IRS)
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CONCLUSIONS:

The explanations and addition information submitted by the sponsor are adequate. The one-year feeding study in dogs should be ungraded from supplementary to core minimum. The referred to study was reviewed in Document Number 007122 and the submitted report is referenced below.

Hellwig,J Report on the Study of the Toxicity of Vinclozolin Beagle Dogs After a 12-Month Administration Via the Diet, by BASF Aktiengellschaft, Dept. Toxicology, 6700 Ludwigshafen/Rhein, West Germany, Study Number 87/0447 of October 1987 (MRID No. 408595-01).

ACTION: Toxicology Branch 1 has been requested to respond to the

sponsor's comments on the required additional information outlined in the DER (Document Number 007122) for a 1-year dog feeding study, Study No. 87/0447, MRID 408595-01.

DETAILS: The requested additional information is listed below. A paraphrase of the sponsor response will follow, and the response of The Toxicology Branch 1 IRS (TB1) will immediately follow the sponsor's response.

The Requested Information:

1. The quality assurance statement must be signed by an appropriate quality assurance official and submitted to the Agency.

2. The results of the data found in the blood smears other than the reticulocytes must be submitted.

3. The source of the dogs used in the study must be submitted.

4. The historical incidence of spontaneous corneal opacity in the strain of dogs used must be submitted.

5. If possible, please explain the high values for the reticulocytes noted in the dogs prior to initiation of treatment.

6. Were there any detectable differences between the control group and the treated group(s) in the male reproductive organs.

7. The numbers in Table C of this DER are assumed to represent reticulocyte counts per 100, but this is not clear in the submitted report. On page 30 (bottom page number) of the submitted report, the unit for reticulocytes are given as unidentifiable symbol, which appears to be "%" sign and ($10^{-3}$ erythrocytes). This should be clarified.

8. The sponsor should present historical control data on the reticulocyte count from the colony of dogs used in this study.

SPONSOR'S RESPONSE TO NUMBER 1:

The Quality Assurance statement is submitted.

TB1 RESPONSE: The signed quality assurance statement is an adequate response to Number 1.

SPONSOR'S RESPONSE TO NUMBER 2:

The values for the white and red blood cell count are in Tables B 261 - B 300 for males and B 301 - B 340 for females. There were no dose related effects.

TB1 RESPONSE: The data referred to should have been in summary tables and in the index or table of contents . The



2

response is adequate.

SPONSOR'S RESPONSE TO NUMBER 3:
The source of the dogs was the breeding facility at BASF Aktiengesllschaft, D-6700, Ludwigshafen, FRG.

TB1 RESPONSE: The response is adequate.

SPONSOR'S RESPONSE TO NUMBER 4:
The historical data on spontaneous corneal opacity in these dogs. Since corneal opacity occurs in controls the one which occur in the HDT can not be considered dose related.

TB1 RESPONSE: The historical control data submitted indicates that unilateral corneal opacity has an incidence of up to 2.7% (range 0-8.3%) in untreated dogs at the beginning of one-year dog studies, and approximately 1.9% (range 0-8.3%) in controls at the end of one-year dog studies. The incidence of corneal opacity in the study on the dog at the HDT of 1/6 (8.3%) and 0/6 (0%) in controls could possibly be compound related. This is especially true considering that corneal opacity occurred in a rat chronic study. However, the incidence of 8.3% in historical controls is at the high end of the range and does not answer the question of whether or not compound related corneal opacity occurred in the dog at HDT.

SPONSOR'S RESPONSE TO NUMBER 5:
A high reticulocyte count for young dogs is not uncommon. When compared to the historical control range the reticulocyte count in dosed groups does not differ from controls.

TB1 RESPONSE: Considering the response to Number 7 below, the apparently high reticulocyte was normal. The explanation is accepted.

SPONSOR'S RESPONSE TO NUMBER 6:
There were no histological effects on the seminiferous tubules, or the prostate. The results on the seminiferous tubules are in Table 166. Pathological examination of the epididymides is not required by the guidelines, but macroscopically, they were not affected.

TB1 RESPONSE: The sponsor's explanation that Table 166 refers specially to histological effects on seminiferous tubules adequately clarifies the problem. With the sponsor's clarification, the hyperplasia referred to in the submitted report was to the seminiferous tubules and not to the Leydig cells. With regard to guidelines and histological examination, the guidelines, 83-1 e(12)(C), indicate that histopathology should be conducted on all target organs in all

animals. The histology seen in the Leydig cells indicates that all male organs of reproduction should be examined histologically. However, the explanation is considered is considered adequate, and the histology is considered adequate for this study.

SPONSOR'S RESPONSE TO NUMBER 7:

The numbers in Table C of your data evaluation report represent reticulocyte counts per 1000. The symbol in the report is "%" which again represents counts per 1000.

TB1 RESPONSE: According to the explanation of Table C in the original 1-year dog study and the report submitted for this action the data should be divided by 10 for conversion to percent. Under these circumstances the apparently high values for the reticulocyte count reported for young dogs when divided by 10 is less than one percent which is neither high nor abnormal. For future reference the symbol "%" refers to the Latin percentum or per hundred, and should not be used to indicate counts per 1000 without an explanation. In this connection, the tables and data in general were ill defined in the submitted report leading to unnecessary ambiguity and /or page flipping.

SPONSOR'S RESPONSE TO NUMBER 8:

The historical control data for reticulocyte count on that Beagle dogs from the laboratory is in Appendix 3.

TB1 RESPONSE: The data submitted are adequate to clarify the problems with the interpretation of the reticulocyte counts in the one-year dog study (MRID No. 408595-01).

TB1 response to sponsor comments on the 1-year dog study/B:\VINCLOZ3.23C\RESSP1YD.OG/D Anderson/9/10/89.