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OFFICE OF PESTICIDES AND TOXIC SUBSTANC

DEC 29 1983

MEMORANDUM:

TO: Henry Jacoby (21)
Registration Division (TS-767)

THROUGH: R. Bruce Jaeger, Section Head
Review Section # 1
Toxicology Branch/HED (TS-769)

SUBJECT: Vinclozolin. RONILAN. EPA Reg. No. 7969-53. 9G2204
Oncogenicity Study in NMRI Mice. CASWELL No. 323C.
BASF Correspondence of August, 1983.

12-29-83

REGISTRANT: BASF Wyandotte Corporation
Parsippany, New Jersey

The registrant submitted their arguments in rebuttal to our finding of oncogenicity of vinclozolin due to lung adenomas in NMRI mice.

The applicant asks, "Does the mouse lung tumor present any special need for more carefully designed analysis of both its biological and statistical significance as compared to other tumor types?"

Our Reply:

We did not subject the mouse tumor data to more detailed scrutiny because of any special concern regarding lung tumors. Indeed, our original special concern had been with the apparent increased incidence in leukemia/lymphoma in male mice, which without tumor data on the three low and intermediate levels showed an apparent increase in incidence between controls and high dose of from 4% (controls) to 20% (high dose). However, after examining leukemia/lymphoma data for all dose levels along with historical control data for the NMRI strain of mouse we noted that the incidence in the treated mice in this study did not exceed the leukemia/lymphoma incidence in many of the historical controls. Also, the incidence was not strictly dose related. Therefore, we believed we could be justified in concluding that it had not been demonstrated that vinclozolin was the cause of leukemia/lymphoma in male mice. However, the stepwise increase in lung adenomas on an apparent dose-related basis in female mice made it more difficult to dismiss lung tumors as resulting from vinclozolin treatment.

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In their effort to demonstrate that the tumors in test mice are not the result of vinclozolin, the applicant points out some of the same observations we had made in our reviews:

1. Because of the weak statistical nature of lung adenomas in female mice only (no statistical significance in males, in rats, or in carcinomas), they believe a careful analysis of the biological significance of the lung adenoma lesion is essential.

2. They refer to Shimkin and Stoner regarding "criticisms that the mouse lung adenoma has no counterpart in 'human neoplastic pathology' and that positive results represent an acceleration process rather than true induction of tumors."

3. The applicant also points out that there generally are no substantial sex differences in tumor incidence. However, in the vinclozolin study, control females showed no lung adenomas and no lung carcinmas, while control males showed 4% lung adenomas and 4% lung carcinomas.

4. In the NMRI strain of mice the incidence of lung adenomas in control females (5 laboratories) ranged from 4.5% to 25.5%. The zero incidence in control females in the vinclozolin study is abnormally low; the incidence of 1/50 in the two low dose groups is also lower than controls in any of the other laboratories; and the incidence of 4/50 and 5/50 in the two high dose groups is within the range seen in the NMRI controls in the other laboratories. In their conclusion they argue that, "we have been able to find no data on vinclozolin that supports the biological significance of the hypothesis that it can induce lung adenoma in the NMRI mouse and would therefore argue that the significance of the trend test results from a single and possibly misleading statistical test in the absence of control tumors (normal average 5.6%) and this compound is not an oncogen. To take data on a non-carcinogen at a dose point without biologic or statistical significance and apply risk assessment methods designed to evaluate life-time carcinogenic findings is a procedure we cannot agree with."

5. To further demonstrate the absence of biological significance of the lung adenomas, the applicant points to the lack of differences in mortality of any of the groups, and the lack of differences in time of lung adenoma development.

6. The applicant points out that as the dose is increased nearly 10-fold from 162 ppm and 486 ppm to 4374 ppm, the incidence of lung adenomas increased from only the non-significant 2% to a slightly significant 10%, a rather flat slope. They state that "most real lung oncogens and carcinogens exhibit a much greater maximal response and very large slope of their dose response curves." They conclude that, "again this finding is consistent with the lack of biological significance of the statistical findings."

7. The applicant also observed that "the fact that no carcinomas were observed even in animals (females) surviving 26 months suggests that vinclozolin has not altered or influenced the normally naturally occuring tumorigenic process in the NMRI mouse which leads to lung adenoma/carcinoma formation. In contrast, for a biological relevant oncogen, it is to be expected that not only the incidence of lung adenoma is increased, but also the progression from adenoma to carcinoma accelerated"

Mutagenicity:

Mutagenicity testing conducted to date yielded positive results on yeasts and fungi. However, this would be expected of a fungicide. A single Ames test (Salmonella) produced a positive finding, but subsequent Ames tests have been negative. The submitted data for a Rec-Assay (Bacillus subtilis) conducted in Japan by Yasuhiko Shirasu, et al., are incomplete. A dominant lethal study in mice and a sister chromatid exchange study in Chinese Hamsters (DNA Repair) were negative. The mutagenicity evidence to data appears to support the non-oncogenicity of vinclozolin, although all the tests may not be adequately reported. Also, we do not have in our files the Ames tests of Prof. Oesch (1977), Chiesara et al., (1982), and BASF Toxicology Dept. (1983). The tests performed by I.E.T. in Japan are inadequately performed or reported.

Conclusions:

After reconsidering the evidence and arguments put forth by the applicant and the data on which these arguments are based, all of which we had recognized previously, we understand their point of view. However we cannot ignore the apparent dose related increased incidence of lung adenomas in vinclozolin treated mice. Even if we consider the expected incidence of lung adenomas in control NMRI mice to be 5.6%, the reliability of the zero (or near zero) incidence of the control mice in this particular test is supported by the near-zero incidence (1/50) in the two low-dosed groups (162 ppm and 486 ppm).

Vinclozolin is not oncogenic in the rat, and for the many reasons cited, is a weak oncogen in the mouse.

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