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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Cyproconazole: Is a Repeat Rat Study Needed for a Carcinogenicity Risk Assessment?

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BACKGROUND

Cyproconazole (a new chemical) has been evaluated by the Health Effects Division's (HED) Carcinogenicity Peer Review Committee (CPRC). The Chemical was classified as a Group C carcinogen, based on liver tumors in male and female mice among other weight of the evidence considerations. The doses used in the mouse study were 0, 5, 15, 100, or 200 ppm; liver tumors were significantly elevated over controls in male mice at 100 and 200 ppm. The CPRC also concluded that the carcinogenic evidence on Cyproconazole was sufficient to carry out a linearized dose response extrapolation to characterize the human cancer risk at low doses of exposure. The Q_1* in human equivalents was originally calculated to be 5.0 E-1 based on the male mouse liver tumors, using the multistage model and adjusting for the shorter study duration (memo June 29, 1990; R. Engler to J. Quest). More recently the Q_1* was re-evaluated, also based on the male mouse liver tumors but using a time-to-tumor model since there were different mortality rates among the dose groups. The Q_1* for Cyproconazole based on the mouse study is now 3.0E-1 (memo June 18, 1992, B. Fisher to L.Taylor).

In the deliberations of the CPRC it was also concluded that the rat study was inadequate, in that the top dose was not high enough to fully assess the carcinogenic potential. It was therefore recommended that the rat study be repeated. The doses used in the rat study were 0, 20, 50, or 350ppm.

REGISTRANT SUBMISSION

The registrant, Sandoz, has made a submission attempting to demonstrate that repeating the rat study would not substantially affect the risk assessment even if tumors were found in the rat above the dose of 350ppm. As a benchmark they first calculated the Q_1* based on the mouse study. The submission offers numerous ways to calculate the potency factor by treating the tumors as fatal or incidental; not surprisingly some the approaches leading to the lower Q_1* values are said to be "biologically" more relevant. However, the highest Q_1* calculated in the submission, based on male mouse liver tumors using the Weibull multistage model incorporating time-to-tumor information, was 2.93E-1, virtually identical to the potency factor of 3.0E-1 calculated by EPA using the same process. The small difference may be due to the fact that the registrant's tumor numbers differ by one (1) tumor for some of the dose groups.

As a next step the registrant "simulated" literally thousands of possible tumor responses at doses above 350ppm. Some of these randomly generated doses as well as tumor responses are very unrealistic, for example a 35/50 tumor response at 352ppm. Additionally, higher doses were postulated which might have been sufficient for a cancer assay. These higher doses were chosen 50, 100, 150, or 200% above the 350ppm actually used in the study. The anticipated tumor response at these doses was chosen at rates ranging from 7/50 (minimally significant) to 49/50 (highly significant). Under either simulation scheme the dose and the corresponding tumor response was added to the existing four (4) dose groups of the rat study for the purpose to calculate a Q_1*. None of the many potency factors thus calculated were greater than the potency factor calculated based on the actual data from the male mouse liver tumor data.

The registrant therefore concludes that the mouse study would remain the critical study for a cancer risk assessment even if a rat study using higher doses should show a carcinogenic response.

EPA SIMULATED RISK ASSESSMENT

In those cases where EPA has carried out a simulated risk assessment we have primarily focused on the proper dose selection for the chronic/carcinogenicity study, i.e. what doses should have been selected based on the toxicological information at hand, e.g 90-day studies. This dose selection uses the best scientific judgement and uses doses which are spaced at intervals of 2-, 3- or sometimes 4-fold increases. The spacing of doses would depend on the overall toxicity of the chemical for which the simulation is carried out, just as it would be the case in an actual dose selection process. The number of selected doses is not limited to three (3) test doses plus control (in a simulated cancer study conservation of animal or monetary resources is not necessary!).

As a next step we have assigned a progressive tumor response to these doses as follows: No increased tumor response was assigned to the NOEL observed in a 90-day study or the highest dose tested in an "inadequate" chronic study. The "background" tumor rate was generally assumed to be 10% or less in control animals and non-responders. At the "lowest" dose where a carcinogenic response was presumed a 40% response rate was postulated and at the next higher dose the presumptive tumor response was set at 80%. We believe that this technique creates a plausible but highly conservative data set, that is, from our experience we conclude that only the most reactive carcinogen would in fact produce this type of dose response.

Specifically for Cyproconazole we would select the following doses for a repeat study: 0, 50, 350, 700, or 1400 ppm. The tumor response at these doses would be simulated as follows: 2/50, 2/50, 2/50, 20/50, 40/50. Using the multistage model of the TOX-RISK program on this data set results in a Q_1^* of 3.4E-2 $(mg/kg/day)^{-1}$.

CONCLUSION

We concur with the registrant, although using somewhat different simulation techniques, that a postulated tumor response in the rat at doses above 350ppm would not alter the quantitative risk assessment for Cyproconazole. In fact it seems that the rat would appear to be at least 10-fold less sensitive to the induction of tumors than the mouse.

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