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MEMORANDUM

SUBJECT: Additional Evaluation of Mammary Tumor Data in Cyromazine Mice and Rats

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Regarding the scheduled (2/24/93) Carcinogenicity Peer Review on **Cyromazine/Melamine** I must comment further regarding the significance of the mouse and rat mammary gland tumors in light of the study data, historical control data, and statistical evaluations which I received on 2/17/93.

With regard to the mammary tumors in Cyromazine rats, please refer to my January 13th Memo in which I stated that the mammary tumors should be considered separately and in combination with other mammary tumors. Important aspects of these considerations are:

- In considering the mammary gland tumors separately, there was no statistically significant ($p \leq 0.05$) pairwise increase in adenomas, fibroadenomas, or adenocarcinomas (at any dose), although there was a statistically significant ($p \leq 0.01$) increased trend in adenocarcinomas.

- In considering combinations of mammary gland tumors, a statistically significant ($p \leq 0.05$) pairwise increase and a statistically significant ($p \leq 0.01$) trend was noted in adenomas and/or adenocarcinomas, although no significant pairwise comparisons or trends were present in adenomas and/or fibroadenomas or in adenomas and/or fibroadenomas and/or adenocarcinomas.

- The incidence of adenomas in the Cyromazine study at any dose (6/14/10/14) was well below the mean historical incidence (38%) of mammary gland adenomas observed in 2-year studies at IRDC (completed between 1978 and 1983) using female Sprague Dawley rats. It should be noted, however, that the range of mammary gland adenomas and fibroadenomas in CRL:CD®BR (Sprague Dawley) rats in 19 two-year studies (1984-1989) was 1.4 - 12.9% and

13.7-49.0%, respectively. (Ref. Charles River Laboratories pamphlet, Feb. 1992) This indicates to me that there may be substantial subjective "overlap" between the diagnoses of adenoma and fibroadenoma.

• The incidence of mammary gland (adeno)carcinomas in the high dose group of Cyromazine rats (15%) exceeded the average historical incidence (12%) but was well within the range (0 - 25%) of incidences of mammary gland (adeno)carcinomas observed in 2-year studies at IRDC (completed between 1978 and 1983) using female Sprague Dawley rats. Other historical incidences of mammary gland (adeno)carcinoma also indicate that 12% is well within the historical range. For example, the historical control range of mammary gland (adeno)carcinomas CRL:CD®BR (Sprague Dawley) rats in 19 two-year studies (1984-1989) was 7.1% - 31.4% with a mean incidence of 17.7%. (Ref. Charles River Laboratories pamphlet, Feb. 1992)

It appears that the significance of the increased incidence of adenomas and/or adenocarcinomas in the rats is driven primarily by the adenocarcinomas. While the incidence of these tumors is within the historical range, the fact that the mouse data also suggest that Cyromazine increases mammary gland adenocarcinomas makes the rat data more biologically significant.

In the mice, the incidence of mammary gland adenocarcinomas in the high-dose females (14%) was statistically significantly ($p \leq 0.05$) increased (pairwise comparison) compared with the vehicle controls (4%). There was also a statistically significant ($p \leq 0.05$) increased trend. The incidence in the high dose group exceeded the range of adenocarcinomas in historical controls (0 - 7.3% [1.7% mean]) in Crl:CD-1®(ICR)BR mice in chronic studies 1978-1985. (Ref. Charles River Laboratories pamphlet) However, when adenoacanthomas were combined with adenocarcinomas (an appropriate grouping), the combined incidences were not statistically significantly increased (pairwise or trend).

Again, as I mentioned in my January 13th Memo, it is appropriate to evaluate tumors separately and combined. In the case of the mouse, the fact that the adenocarcinomas and/or adenoacanthomas are not statistically significantly increased does not negate the fact that the adenocarcinomas alone are statistically significantly increased. In addition, because there is an indication that Cyromazine causes an increase in rat mammary adenocarcinomas, the mouse data is made more biologically significant.

One final thought concerns body weight. In the Cyromazine rat study, both absolute body weight and body weight gain were markedly reduced in the high dose group compared to controls. As I mentioned in my January 13th Memo, studies suggest that this may have lowered the incidence of benign mammary tumors (fibroadenomas and/or adenomas). It is mere speculation, but had there not been such a decrease in body weight, the incidence in adenomas may have been increased as the adenocarcinomas were.

These mammary gland tumor data are not easy to evaluate. My feeling is that there is weak evidence that Cyromazine causes an increased incidence of mammary gland adenocarcinomas. The CPR meeting should be interesting.