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ADDENDUM TO DATA EVALUATION REPORT

STUDY TYPE: Mouse oncogenicity

GUIDELINE #: 83-2

MRID #: 421783-10

TEST MATERIAL: S-31183

SYNONYMS: Sumilarv

STUDY NUMBERS: 343-215

SPONSOR: Sumitomo chemical
Osaka, Japan

TESTING FACILITY: Hazelton Laboratories
Vienna, Virginia

TITLE OF REPORT: Sumilarv - Oncogenicity Study in Mice with S-31183

AUTHORS: Merrill Osheroff, PhD

REPORT ISSUED: July 23, 1991

Discussion:

This addendum serves to clarify points made in the primary review pertaining to the acceptability of the data based on the overall health status of the test animals. The primary reviewer feels that the finding of systemic amyloidosis compromised the study in that it was indicative of intercurrent infections within the test groups.

Comments on Health Status of Test Animals

The reviewer states in his report that many of the deaths throughout the treated and control groups were associated with sepsis, infection and inflammation. This statement is not accurate. Of the unscheduled deaths that occured during the 18 month study the number associated with sepsis, infection and/ or inflammation were **2/50, 5/50, 3/50 and 4/50** for control, low dose, intermediate dose and high dose males, respectively. For females the distribution was **1/50, 2/50, 2/50 and 0/50** for control to high dose groups, respectively. For several animals which died during the course of the study, a cause of death could not be determined

because post-mortem autolysis had occured. These deaths which could be associated with sepsis, infections etc. occured sporadically throughout the study and could not be traced back to any specific etiology.

If the test animals had dubious health that was compromised by infections, the number of animals affected would have been higher, the deaths would not have been sporadic (deaths probably would have occured within the same time frame) and the survivability would probably have fallen below the requisite 25% for all groups (not just for the high dose males) at the end of the study.

Comments on Incidence of Amyloidosis and Early Deaths

Amyloid is a prevalent finding in aged CD-1 mice. The incidence of this condition in susceptible strains has been reported to be as high as 100%. The presence of this condition is not believed to have compromised this study because the oncogenic potential of the test material could still be determined with the number of survivors.

Even though there appears to be a dose related increase in the number of deaths, this finding is not believed to be substantial, in that a variety of causes have been linked to the so-called early deaths, none of which implicates the test substance. If the impact of the test material on the presence and severity of amyloidosis is analyzed, it is apparent that there is no increase in the incidence of this condition in treated males and a questionable increase in the incidence of systemic amyloidosis in high dose females.

Conclusions:

There were no systemic effects present during the study that could be associated with the test material. As discussed above, the mortality rates for treatment groups do not appear to be related to the administration of the test material.
The study should be classified as supplementary. In the absence of systemic effects and body weight and body weight gain decrements at the highest dose tested, it is felt that an MTD was not reached. The study should therefore be repeated at higher dietary dose levels. A NOEL has not be determined.