April 27, 1995

EPA-SAB-EHC-COM-95-002

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Subject: Science Advisory Board's Commentary on the EPA's use of the Benchmark Dose calculation method.

Dear Ms. Browner:

At the April 6, 1994 meeting of the SAB's Environmental Health Committee (EHC), the Committee was briefed by staff from the Office of Research and Development (ORD) on the Agency's progress in analyzing the "Benchmark Dose" method as an alternative to the current "NOAEL/LOAEL (No Observed Adverse Effects Level/Lowest Observed Adverse Effects Level) approach for calculating reference dose (RfD) levels. The Committee has long advocated the study of this methodology, and has stated its view of the advantages of the Benchmark approach in several previous advisory documents.[1]

During the briefing, Staff informed the Committee that a "White Paper" on the Benchmark approach was being prepared and would be available for SAB for review in the future. In its subsequent discussions, the EHC identified some key issues which it believes are critical to developing both a full understanding of the benchmark methodology and its eventual

[1] Environmental Health Committee, U.S. EPA Science Advisory Board, 1990. *Use of Uncertainty and Modifying Factors in Establishing Reference Dose Levels.* EPA-SAB-EHC-90-005; Environmental Health Committee, U.S. EPA Science Advisory Board, 1993. *Review of the Office of Solid Waste and Emergency Response's Draft Risk Assessment Guidance for the Superfund Human Health Evaluation Manual*. EPA-SAB-EHC-93-007.

implementation, and which should be addressed in any future Agency statements on this topic. Specifically, the EHC recommends that the Agency:

a) Examine and assess the comparability of the Benchmark and current NOAEL/LOAEL calculation for many data sets, involving different types of toxicity and routes of exposure. This work should extend the recent efforts sponsored by the Agency on developmental toxicity[2] and should compare NOAEL and benchmark calculations obtained both from individual data sets and data set(s) used to define the "critical effect." The Committee would also be interested in seeing comparisons between the benchmark and NOAEL calculations and results obtained using threshold and non-threshold extrapolation models.

b) Comment on the effects of the underlying experimental design on the results of the benchmark dose calculation, as well as on the range of doses needed to characterize the dose response curve.

c) Address methodology for dealing with situations where dose-response data may not be monotonic in form. The Committee is aware that dealing with non-monotonic data is (in this context, and with the NOAEL/LOAEL approach as well) very difficult, and that in fact, no good methodology may yet be available. Nonetheless, we believe that the White Paper should at least deal with the issue and perhaps suggest some possible approaches.

d) Comment on the differential impacts on the benchmark dose calculation of using various types of data sets. Specifically, dose-response data sets underlying a benchmark dose calculation may be of a continuous or quantal type, and require differing approaches for their use.

Developing a full understanding of the Benchmark dose and the data requirements for valid use of this methodology would contribute to the EPA's goal of providing credible science in

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[2] Faustman, E., Allen, B., Kavlock, R., and Kimmel, C. 1994. Dose-response assessment for developmental toxicity--characterization of database. *Fund. and App, Tox.*, 23, 478-486; Allen, B. Kavlock, R., Kimmel, C., and Faustman, E. 1994. Dose-response assessment for developmental toxicity --comparison of generic benchmark dose estimates with NOAELS. *Fund. and App. Tox.* 23:487-495; Allen, B. Kavlock, R., Kimmel, C., and Faustman, E. 1994. Dose-response assessment for developmental toxicity--statistical models. *Fund. and App. Tox.* 23:496-509

support of the risk assessment process. Consequently, we again wish to encourage the Agency to proceed vigorously in its review and development of this approach. We look forward to your response to these recommendations.

Sincerely,

Genevieve M. Matanoski

Dr. Genevieve Matanoski, Chair
Science Advisory Board

Frederica P. Perera

Dr. Frederica Perera, Chair
Environmental Health Committee

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