DRAFT

Responses to Major Comments on Technical Support Document

Public Health Goal
For
Barium
In Drinking Water

Prepared by

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DRAFT

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INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for barium as discussed at the PHG workshop held on July 22, 2002, or as revised following the workshop. Some commenters provided comments on both the first and second drafts. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from Health and Ecological Criteria Division, Office of Science and Technology/Office of Water, U.S. Environmental Protection Agency (Edward V. Ohanian)

Comment 1: "In many of the early references to the NTP study in this document, the specific barium salt used was not identified. In addition, there was no discussion of any possible mechanism through which barium induces hypertension. If there are data regarding mode of action they would be a valuable addition to the document."

Response 1: In the description of the NTP (1994) study, we state that barium chloride was the toxicant administered. Barium induced hypertension is primarily due to muscle stimulation due to a blocking of calcium-activated potassium channels that control cellular potassium efflux. Thus, barium intoxication results in a rise of intracellular potassium and a corresponding drop of extracellular potassium, leading to hypokalemia (Goyer and Clarkson, 2001). This has been added to the text of the PHG document.

Comment 2: "Is there any indication if insoluble barium is taken up from the lung by phagocytosis?"

Response 2: In their study on dogs, Morrow *et al.* (1964) mentioned phagocytosis as one of the possible mechanisms of the second clearance phase of insoluble barium sulfate dust from the lower respiratory tract. This has been added to the document.

Comment 3: "I found the discussion of the Dietz *et al.* (1992) one-generation study difficult to follow. For example, which females (dams or pups) were terminated on days 96 and 97? Why does the conclusion only apply to males? Was there any reason that could explain low pregnancy rate in exposed and control animals?"

Response 3: The discussion of the reproductive and fertility evaluation portion of the Dietz (1992) study was expanded for increased clarity.

Comment 4: *For the cited study Perry et al. (1983), clarify as to whether doses are "uptake" or "intake" and whether 0.17 mg/kg-d was a LOAEL or NOAEL value.*

Response 4: We agree that this was confusing; for the description of Perry *et al.* (1983), "uptake" has been changed to "intake" and it is stated that 0.17 mg/kg-d is the NOAEL.

Comment 5. *The commenter suggested some minor, clarifying text changes in both the Wones et al. (1990) and the Brenniman and Levy (1984) study descriptions.*

Response 5: Changes have been made.

Comment 6: "It is EPA's judgment that a 3-fold uncertainty factor is sufficient when applied to the data from two human studies which, between them, examined a cross section of the adult population and which identified a NOAEL but not a LOAEL."

Response 6: This was the most frequent of all the substantive comments received (see also comments from two of the three UC reviewers). Our original rationale for an uncertainty factor of 10 included 3 for intra-human variability and 3 for data limitations. Following further review, we concur with the majority of commenters that, especially for a PHG value based upon a freestanding NOAEL from a human study, not supported by a human LOAEL, an uncertainty value of 3 is appropriate.

Comments from Departments of Environmental Toxicology and Nutrition, University of California Davis, Bodega Marine Laboratory (Gary N. Cherr, Ph.D.).

Comment 1. *The reviewer recommends some discussion on additional mechanisms of barium toxicity; and suggests a few pertinent journal articles.*

Response 1. Of the recommended articles, the1989 study by Taglialatela *et al*. provided a straightforward *in vitro* example of how barium can act independently from calcium ions, and stimulate dopamine release from tuberoinfundibular neurons in a dose-dependant manner. A brief discussion of this study has been included in the neurotoxicity section of the document.

Comments from University of California-Davis (Professor Emeritus Marvin Goldman)

Comment 1. "The case is not made as to why California has settled on a level three times more restrictive than the EPA. I think that California should explain why the national standard is too high and where EPA used the "wrong" analysis, since both rely on the same two human studies (Wones and Brenniman). The use of an UF of 10 appears too conservative; a factor of three is more often the case in elements such as barium. The calculation of the PHG should include an uncertainty factor of three, but it is not likely that an additional factor of three for sensitivity variability is needed. In view of the extensive literature on alkaline earth metals is not likely that there are subsets of the population that are especially sensitive to barium intoxication."

Response 1. After reviewing the rationale for uncertainty factor selection, we concur with the commenter and have changed the value to three.

Comments from the Center for Health and the Environment, University of California, Davis (Hanspeter Witschi, M.D.).

Comment 1. "With regard to uncertainty factors, this reviewer would concur with the U.S. EPA position, although OEHHA makes a good point for its selection."

Response 1. After reviewing the rationale for uncertainty factor selection, we concur with the commenter (and the U.S. EPA) and have changed the value to three.

Comment 2. "Page 6, first 8 lines: this paragraph is in direct contradiction with page 1, lines 3-5 in "Introduction" that explicitly states "Barium sulfate, which is highly insoluble, has commonly been used....". Were there tracer amounts (e.g. carrier free Ba) used in the studies by McCauley and Washington?"

Response 2. The paragraph was expanded to mention that barium sulfate was administered as a suspension.

Comment 3. "Page 9, first sentences: why was there a shift in barium doses? Less water intake, growth? Needs to be explained."

Response 3. The paragraph was expanded to explain that the shift in dose occurred from a combination of animal growth and decrease in water uptake (high dose level).

Comment 4. "Page 17, line 8 in "Noncancer effects": epidemiological rather than ecological studies?"

Response 4. Changed *ecological* to read *environmental epidemiological* to avoid this confusion.

Comment 5. "Page 19, line 4: usually it is animal studies that provide some uncertainty with regard to extrapolation to man - why in this particular case does the selection of human studies over animal research create some uncertainty? The logical extension of this statement would be to eliminate the uncertainty by selecting the animal data!"

Response 5. The commenter is correct. The line in question was rephrased to read "An additional area of discussion is the selection of human studies over the animal research."

Comment 6. *The reviewer commented that there seemed to be too much reliance on the secondary literature.*

Response 6. After further literature review and a few revisions to text, secondary citations were directly attributed to the primary references.

REFERENCES

Goyer R and Clarkson T (2001). Toxic Effects of Metals, Chapter 23. Klaassen, C, ed. Casarett and Doull's Toxicology – The Basic Science of Poisons, Sixth edition, McGraw-Hill, New York.

Taglialatela M, Canzoniero L, Amoroso S, Fatatis A, Di Renzo G, and Annunziato L (1989). Cobalt sensitive and dihydropyridine-insensitive stimulation of dopamine release from tuberoinfundibular neurons by high extracellular concentrations of barium ions. Brain Res 488(1-2):114-20.