

Monsanto

Monsanto Chemical Company
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October 11, 1989

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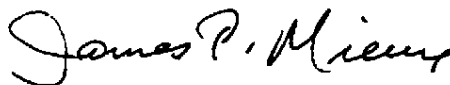
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P.A. Gilbert - Unilever
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C.A. Pittinger - P & G (U.S.)

Dear Colleague:

Dr. Ellen Robinson of Monsanto's toxicology staff has submitted an abstract on genotoxicity testing of LAB for presentation at the 1990 Society of Toxicology meeting February 12th through 16th in Miami Beach. A copy of the abstract is attached for your information. As you can see, all tests were negative.

We can review these results with you at the skin painting meeting tentatively scheduled for November 20th and 21st.

Sincerely,



James P. Mieux
Manager, Product Safety

cc: C.B. Beckmann - G4WA
R.D. Hogue - O4B
T.M. King - O4C
E.C. Robinson - A3ND

genotst.ltr

VVV 000014267

THE GENOTOXIC POTENTIAL OF LINEAR ALKYL BENZENES
IN A SHORT TERM TEST BATTERY. E.C. Robinson¹,
R.S. Nair¹, J. Gridley¹, J. Cavagnaro², T.
Cortina², and E.H. Godek³; Monsanto Co.¹,
St. Louis, MO, Hazleton Laboratories of
America², Vienna, VA, and Pharmakon Research
International³, Waverly, PA.

Alkylate 215 (A-215), Alkylate 225 (A-225) and
Alkylate 230 (A-230) are mixtures of C₁₀-C₁₆
linear alkylbenzenes used as intermediates for
the manufacture of detergents. These products
were evaluated for genotoxic activity in the
Ames bacterial mutagenesis assay (strains TA98,
100, 1535 and 1537), the CHO/HGPRT mammalian
cell forward gene mutation assay, and the in
vivo rat bone marrow chromosome assay. The
Ames and CHO/HGPRT assays were conducted both
with and without the addition of Aroclor-induced
rat liver S9. The maximum concentrations
evaluated were 10 mg per plate (A-215) and 3 mg
per plate (A-225 and A-230) for the Ames test,
and 1.5 mg/ml (A-215 and A-225) and 2.0 mg/ml
(A-230) for the CHO/HGPRT assay. In each case,
the highest concentrations produced evidence of
either toxicity or insolubility. The highest
dose in the bone marrow cytogenetics assay was
12,700 mg/kg, a level which produced weight
loss. The results of all tests were negative,
indicating a lack of genotoxic activity as
measured by the battery of tests used.

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Tickle
10/16

FROM

(NAME-LOCATION-PHONE) James P. Mieux (G4WR) (4-4837)

DATE: September 29, 1989 cc: C. Beckmann - G4WA
T.G. Grumbles - Vista (Houston)
J.S. Harding - 5040
F.E. Kearney - G4WT
T.M. King - 04C
J.C. Ledvina - Vista (Houston)
A.M. Nielsen - Vista (Austin)
F.C. Roheim - Vista (Austin)

SUBJ: Skin Painting

REF:

TO: R.D. Hogue

This memo provides an update on LAB skin painting developments.

1. The first Iversen manuscript was published earlier this month in the British Journal of Industrial Medicine. I have ordered a copy, which I will distribute. I believe the paper is essentially identical to the last draft we saw. Shell was unsuccessful in getting their mutagenicity studies included, but ours are cited.
2. With our encouragement, P&G's George Calvin has made progress in coordinating an industry preparedness program. He met twice with Bill Fernley to outline potential elements of the program. These elements are the same as Calvin and I developed in July (see my July 28 memo). In summary, the potential activities include publishing comments on Iversen's procedure, publishing guidelines for proper conduct of chronic skin studies, publishing results of industry mutagenicity studies, conducting a dermal uptake, metabolism and pharmacokinetic study, conducting an epidemiology study on Scandinavian electrical/telephone workers and conducting a chronic dermal study utilizing proper protocol. These activities represent a range of effort, expense and timing issues and should provide a challenging exercise in cost/benefit analysis. Calvin appears to favor doing all components, while Fernley (and ECOSOL?) have finally gotten involved and are supporting at least the publication aspects. My initial reaction is to support all publications and to conduct the dermal metabolism/pharmacokinetic and epidemiology studies. I think they can be conducted in a reasonable time frame and at reasonable (shared) expense. It is not clear to me how a dermal chronic study would justify the cost. Results would not be available for 3+ years from initiation of the study; I believe the skin painting issue will be decided before then, either by attrition /apathy or because some group will press the issue. To date our involvement has been to stress the need for preparedness and to indicate our openness to look at alternatives. We have not committed to any studies. The price tag for all studies would probably exceed \$1,000,000.

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3. In a 9/26 conversation with Calvin he indicated need for feedback from Vista and Monsanto on our willingness to meet to discuss the total program and the merits of additional studies. Such a meeting would presumably involve P&G, Unilever and ECOSOL, and possibly Essochem. We have proposed November 20 and 21 as possible dates, which would piggyback on the Berlin Workshop. Tom, are you still agreeable to such a meeting and are those dates OK?
4. According to Calvin, Fernley has proposed a cost sharing formula for any additional studies. He proposed all studies be split into four shares, one to be paid by ECOSOL, one by CLER, one by P&G and one by Unilever. Calvin indicated P&G is not pleased with this proposal, but at least it is a point of departure. Fernley has not directly mentioned any financial arrangements to me.
5. Fernley will be in the U.S. in early November and may try to convene a November 2 meeting with Vista and Monsanto representatives on skin painting.
6. Keith Huckle of Shell phoned in response to Monsanto's offer to discuss optimum arrangements for publishing mutagenicity studies. Preliminary discussions suggest two back-to-back articles in the same scientific journal might be preferable to a joint publication, since test conditions and test chemicals were different. We plan to share preliminary drafts in a few weeks.
7. Huckle indicated Iversen is behind schedule on completing his next manuscript, which will include data on LAB. The manuscript already exceeds 100 pages, which would force Iversen to go to a journal which uses a monograph format. Iversen is currently on sabbatical, which has slowed his writing. He has indicated his intent to send a copy of this second manuscript to the International Agency for Research on Cancer (IARC) concurrent with journal submission. IARC's charter includes preparing cancer risk assessment monographs. These are usually fairly well-balanced and take into account all published, peer reviewed data. This makes publication of our genotoxicity data especially important, on the slight chance that IARC might become interested in LAB.
8. A contingent from P&G and Shell plans to visit Iversen to be certain he is aware that guidelines for conducting chronic dermal studies have changed and that his techniques are out of date (possibly saving him future embarrassment).
9. Tom Grumbles, I and our respective toxicologists plan a conference call in about two weeks to discuss the pros and cons of the potential tests mentioned above.

Things are starting to happen!



J.P. Mieux

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