SEP 17 1973

Litton BIONETICS

7315 Wisconsin Avenue, Bethesda, Maryland 20014 301 881-5600

September 17, 1973

Dr. Kenneth D. Johnson
Assistant Technical Director
Occupational Health
Manufacturing Chemists Association
1825 Connecticut Avenue, N. W.
Washington, D. C. 20009

Dear Dr. Johnson:

As I mentioned to you on the phone, members of our staff have given considerable thought to your request for a proposal to perform a preliminary feasibility study for the incorporation of vinyl chloride monomer in the diet or drinking water of laboratory animals.

While we have evaluated several ideas, we did not come up with one where we felt we could be strongly confident of success. As a result, we did not provide a reply to meet your early September date. However, our staff feels that we do have capability to perform the other phases of your requirement if a division of this program is feasible. It is difficult to propose at this time a definitive method to determine storage stability of the diet since complete information concerning the components of the diet matrix is not available. A probable approach would be extraction of the vinyl chloride monomer with a suitable organic solvent followed by gas chromatographic analysis. It is recognized that, because of the physical characteristics of the monomer, extensive sample workup to remove possible interferences may be extremely difficult, if not impossible. It is our opinion that absorption of ingested monomer may be demonstrated best by using isotopically labelled material. Extent of absorption would be determined by radioactive measurement of the test animal's blood, excreta and expired air (if 14 C is used).

Thank you for giving Litton Bionetics the opportunity of responding to this request, and we would be most happy to perform a part of the program. If a satisfactory technique is developed, we would welcome the opportunity of providing a proposal for the animal toxicity study.

Sincerely,

Harvey E. Giss

Harvey E. Giss
Manager
Program Development

HEG:BEM

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Reply to
WAVERLY DIVISION
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P.O. Box 107
Waverly, New York 14892
(607) 565-2931

September 5, 1973

Dr. Kenneth D. Johnson
Division of Occupational Health
Manufacturing Chemists Association
1825 Connecticut Avenue, N.W.
Washington, D.C. 20009

Dear Dr. Johnson:

As indicated in his recent telephone conversation with you, Dr. Oser has asked me to confirm our interest in undertaking feasibility studies aimed at establishing a technique for incorporating vinyl chloride monomer (VCM) in animal diets at controlled levels of exposure. We are, of course, familiar with the background which prompts your request of July 30th. We have delayed this response for a few days in order to gain advantage of the information presented in a symposium sponsored by the Division of Organic Coatings and Plastics Chemistry of the American Chemical Society at its meetings in Chicago last week. The subject of the symposium was microencapsulation which is, in our opinion, the only available technique which shows promis of providing a successful answer to the problem.

It would be our choice to investigate a series of shell-forming systems using the interfacial polymerization method to achieve a capsule membrane having controllable diffusion constants for VCM from an oil solution in a finite range. This range would be determined by considerations of the obtainable concentration gradient, the character of the encapsulated vehicle, shell thickness, and the effects of temperature. The first objective would be to produce microcapsules in the 50-200 micron range which would have a relatively constant VCM release rate over at least a 48-72 hour period that would provide the equivalent of 250 ppm of the monomer in the total diet.

Obviously, the final rat diets would have to be prepared fresh daily using capsule levels calculated from the previously established decay curves for their VCM content. The encapsulation process would also have to be repeated at frequent intervals to ensure a constant supply of material for dietary incorporation.

This approach does not envisage any appreciable disintegration of the capsule wall within the digestive tracts of the animals. Rather, exposure will occur through slow, controlled diffusion of VCM from the microcapsules into the digesta with whatever ensuing

interaction and absorption may take place. Gas chromatographic methods of analysis are available with sufficient sensitivity to make monitoring of both the intake and the excretion of VCM possible. However, it will probably be necessary to conduct at least one trial in animals using ^{14}C-tagged VCM since it is highly likely that a considerable proportion of the available monomer will react with tissue components or gut contents and ultimately undergo degradation or excretion in some combined form. This confirmatory experiment would be necessary to permit full evaluation of the procedure and the data obtained therefrom.

It is obvious that although the existing technology appears to promise a reasonable chance of succeeding, a number of variables will have to be evaluated on a trial-and-error basis. The best combination of carrier vehicle, shell-wall composition, shell thickness, and microcapsule size must be determined empirically. A laboratory scale set-up must be designed and standardized to permit on-site production of adequate supplies of microencapsulated VCM. The analytical methods available must be calibrated and/or modified to be applicable to both diets and excreta.

We would be pleased to undertake the investigations outlined herein in collaboration with members of your technical committee. The "best-efforts" fixed fee would be $11,000 over a period not to exceed 120 days during which we would be available for consultation at any time and issue monthly written progress reports. If it is mutually agreed that extension of the work beyond the 120th day would be in the best interests of MCA, we would continue at a monthly fee of $2500, subject to renewal on a month-by-month basis.

If this proposal appears to merit further discussion, we would be glad to meet with you and your colleagues for that purpose. Please do not hesitate to call with any questions or comments.

Cordially,

FOOD and DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

KM:smm

Snell

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August 31, 1973

Dr. Kenneth D. Johnson, Ph.D.
Assistant Technical Director
Occupational Health
Manufacturing Chemists Association
1825 Connecticut Avenue, N.W.
Washington, D. C. 20009

Dear Dr. Johnson:

This proposal is in response to your letter of July 30, 1973 to Mr. J. W. Taylor requesting a bid on a proposed feasibility study designed to establish safe residue levels of vinyl chloride monomer in foods and/or beverages.

You have correctly pointed out the potential dosage error factors which may arise from incorporating a highly volatile material such as vinyl chloride monomer into the usual diet or drinking water. But, of course, many "tricks" can be used to prevent such loss and thus ensure a predictable ingested dose.

For clarity we shall review in more detail each point mentioned by you.

1. Rat rations containing known concentrations of vinyl chloride monomer (up to 250 ppm VCM) may be prepared as follows:

   a. Microencapsulation

      The vinyl chloride gas may be microencapsulated in a moderately soft fat (tallow or margerine) using a coacervation technique (gelatin) or another microencapsulation method.

   b. Adsorption

      As an alternative to the above the vinyl chloride may be adsorbed on such materials as ion-exchange resins, charcoal, silica gel, etc. The vinyl chloride gas will be released at the acid pH of the stomach.

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c. Solution

Vinyl chloride monomer is soluble in alcohol and thus it should be possible to incorporate the gas into a glycerol/water mixture. Hopefully a level of glycerol can be established which will maintain appropriate concentrations of VCM for adequate dosing using reasonable quantities of water. If necessary, this amount could be administered by gavage. This procedure could be most appropriate since it resembles the manner in which VCM normally enters the body following extraction by alcoholic beverages.

2. Determine the storage stability of the diet, both in closed containers and in the feed pans and/or water dispensers. This problem is actually an extension of Phase 1 and is intended to ensure that the VCM remains in the feeding vehicle for as long as necessary between preparations of feed batches or water for drinking.

3. Demonstrate absorption of the ingested dose.
This phase represents a bioavailability type of test. Groups of rats will be administered VCM by gavage in an aqueous solution, and blood levels measured over a period of one to six hours. Comparison will then be made with another group administered VCM by the method selected for Phase 1. Blood will be taken from the orbital sinus in a time sequence to be followed in the same animal. Ten animals will be used in each group. VCM will be measured in serum by gas chromatography utilizing for detection either (a) thermal conductivity, (b) flame ionization, or (c) electron capture. Use of C^{14} tagging will also be explored.

4. Quality control methods.
Appropriate sampling of the prepared diets will be made initially and after several days storage to determine if the appropriate VCM levels are present. It would also be important to measure certain key vitamin levels since VCM may interact with vitamins thus producing a vitamin deficient diet.

5. The problems of working with VCM are obvious and we need not oversimplify them; however, with proper care, no major difficulty should be encountered.

The cost of the proposed feasibility study as a fixed price on a "best effort" basis would approximate $14,500.

POLICY AND CONDITIONS

This assignment is specifically accepted under the following terms and conditions:

- FDS performs all services for its clients on a best efforts basis. In addition, any confidential information received from its clients as a result of an assignment is held by FDS in strictest confidence and is not disclosed to anyone other than the necessary members of the staff of FDS, except on specific authorization from the client.

- FDS reports are submitted to its clients for the client's sole use. Any use of all or any portion of the report(s) in any manner of advertising or public announcement without the express written permission of an officer of FDS is prohibited except as may be required by law.

- Title to all inventions, whether or not patentable, conceived or developed by FDS under this Agreement shall vest solely in th client and shall become its exclusive property only to the extent that these inventions are specifically directed to the assignment which is the subject of this Agreement.

- No express or implied warranty is made for results or interpretations, except for types of analysis and testing which employ published, accepted, clearly defined, standard methods (U.S. Pharmacopeia, A.O.A.C. and A.O.C.S. methods...). In the event that results, conclusions or recommendations from such analytical or testing work are proved to be erroneous, the liability of FDS, or its subsidiaries, shall not exceed the fee charged for that part of the information which has been found to be in error.

- FDS shall save and hold its clients harmless against all claims for injury to person or damage to property arising out of the negligent acts of members of FDS's staff during the actual period of the performance of services under this Agreement; moreover, FDS further agrees to maintain insurance to cover any such claims.

- Clients shall save and hold FDS harmless against all claims for injury to person or damage to property arising out of and during the course of:

  .. Assignments in which, with the prior knowledge of the client, human subjects are used for testing and evaluating a product or products or process, or

  .. The testing, evaluation, and use of any and all products or processes manufactured or furnished by the client, or

  .. The use of any and all products or processes developed by FDS for the client when FDS no longer has absolute control over such formulation, development, or manufacture, or

  .. The period of time subsequent to the date of completion of the assignment;

  .. moreover, the client further agrees to maintain insurance to cover any such claims.

- The client represents and warrants to FDS that it is duly authorized and empowered to enter into this Agreement and the funds are available for payment to FDS hereunder, both without the further consent or authorization of any other person or organization.

- Failure of the client to accept the independent conclusions or recommendations of FDS on the basis of differences of opinion in judgmental areas shall in no way be construed as a failure on the part of FDS to meet the requirements of this Agreement or provide a basis for disapproval or non-payment of monthly invoices.

- Charges to clients are comprised of fees for professional services rendered plus reimbursement of expenses incurred as a result of

If we can be of any further service please do not hesitate to call upon us.

Very truly yours,

A. Leonard Sheffner

FOSTER D. SNELL, Inc.

A. Leonard Sheffner, Ph.D.
Vice President

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