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Public Affairs Committee
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TO

FROM

J. F. Welch

J. F. Welch, Director, Public Affairs

Internal Correspondence

DATE November 5, 1981

SUBJECT NIEHS Animal Feeding Studies

REF: JFW correspondence, same title, February 6, 1981

ACTION REQUIRED: Review for information

Enclosed are summary minutes of the National Toxicology Board of Scientific Counselors' peer review (June 23, 1981) of the carcinogenesis bioassay of asbestos fed to Syrian golden hamsters. They state:

... Under the conditions of the bioassay, the ingestion of short range (S.R.) and intermediate range (I.R.) chrysotile asbestos was not carcinogenic in male and female Syrian golden hamsters.

Similar conclusions are drawn with respect to amosite asbestos.

These findings are reiterated in NTP Technical Bulletin Issue No. 5, August, 1981, also enclosed.

If you have any questions, please do not hesitate to call.

JFW/ajb

Enclosure

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NTP TECHNICAL BULLETIN

NATIONAL TOXICOLOGY PROGRAM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

Issue Number 5

August 1981

Director: David P. Rall, M.D., Ph.D.
Deputy Director: John A. Moore, D.V.M.

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CURRENT APPROACHES TO TOXICOLOGICAL CHARACTERIZATION -- A principle objective established for NTP is to broaden the toxicologic characterization of chemicals selected for testing. This is being effected by initiating a series of toxicology studies to be performed as part of, or concurrent with, the prechronic phase of animal testing. The purpose of these procedures is to define time and dose related toxicity, identify target organ systems, and determine the highest dose that will not cause overt toxicity in a two-year study. After a review of the composite results, the program can more effectively assign priorities to those chemicals that require added testing. The experimental protocol for additional tests can be specifically designed to focus on toxicologic and carcinogenic parameters of specific interest. Current NTP procedures include:

Chemical Disposition -- In most instances basic information on the absorption, tissue distribution, routes of excretion, and degree of metabolism are determined in the rat using radiolabeled chemicals. This data will permit more informed decisions on appropriate route and dose for additional (chronic) animal testing.

Clinical Data -- More extensive data on body weight gain and food consumption are being collected. Hematology and urinalysis are routinely performed in the subchronic phase of testing. Clinical chemistry procedures that assess liver or kidney functions are frequently required. Other selected procedures, such as thyroid functions, methemoglobin levels, are also incorporated when appropriate.

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Table 3
NTP CARCINOGENESIS BIOASSAY RESULTS ON EIGHT CHEMICALS (a)

Chemical (CAS Registry Number)	Testing Laboratory	Use	Route	Results Under Bioassay Test Conditions
Allyl Isothiocyanate (57-06-7)	Southern Research Institute	Flavoring agent, major component in brown mustard seed	Gavage	Carcinogenic in male F344 rats inducing transitional-cell papillomas in the urinary bladder, and epithelial hyperplasia in urinary bladder of male rats that did not have papillomas; evidence for inducing subcutaneous fibrosarcoma in female F344 rats is equivocal; not carcinogenic for B6C3F1 mice of either sex; increased cytoplasmic vacuolization in livers of male mice
Asbestos, Amosite (12172-73-5)	Illinois Institute of Technology Research Institute (IITRI)	Asbestos cement pipe	Feed	Not carcinogenic in male or female Syrian golden hamsters
Asbestos, Chrysotile (12001-29-5)	IITRI	Asbestos cement, textiles, insulation	Feed	Not carcinogenic in male or female Syrian golden hamsters (short range or intermediate range asbestos)
Asbestos, Chrysotile (12001-29-5) and 1,2-Dimethylhydrazine (540-73-8)	IITRI	Positive control (intestinal carcinogen)	Feed	Combination study inadequate (intermediate range asbestos and DMH); no increase in DMH-induced intestinal neoplasia
2-Biphenylamine Hydro- chloride (90-41-5)	EG&G Mason Research Institute	Chemical intermediate for C.I. Acid Red 15	Feed	Carcinogenic for female B6C3F1 mice inducing angiosarcomas; not carcinogenic for male mice (poor survival may have contributed to lack of statistical evidence); not carcinogenic for F344 rats of either sex
Pentachloroethane (76-01-7)	Gulf South Research Institute	Solvent; formerly intermediate for tetrachloroethane manufacture	Gavage	Not carcinogenic for F344 rats of either sex; nephrotoxic for male rats; carcinogenic for male B6C3F1 mice inducing hepatocellular carcinomas and female B6C3F1 mice inducing both hepatocellular carcinomas and adenomas
Polybrominated Biphenyl Mixture (Firemaster FF-1) (67774-32-7)	Battelle Columbus Laboratories	Flame retardant	Gavage	Carcinogenic for Fisher 344 rats and B6C3F1 mice of both sexes, inducing neoplastic nodules, hepatocellular carcinomas and cholangiocarcinomas in rats and hepatocellular carcinomas in mice; other toxicities include porphyrogenic effects and hepa- totoxicity in both species, affected body weight gain in rats and male mice
Stannous Chloride (7772-99-8)	Southern Research Institute	Food preservative, reducing agent in tinplating, stabilizer (colors, perfumes, soaps)	Feed	Not carcinogenic for F344 rats or B6C3F1 mice of either sex

(a) Bioassay reports reviewed at the 23 June meeting of the NTP Technical Reports Peer Review Panel will be available from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161, Tel. 703-487-4650 following notice in the Federal Register. Requests for information about the NTP Technical Reports should be directed to the Technical Information Section, Room 3A06, Landow Building, Bethesda, MD 20205, Tel. 301-496-1152.

2. Chrysotile Asbestos. Dr. Swenberg, as the primary reviewer for the report on the bioassay of chrysotile asbestos, agreed with the conclusions that, under the conditions of the bioassay, the ingestion of short range (SR) and intermediate range (IR) chrysotile asbestos was not carcinogenic in male and female Syrian golden hamsters. The asbestos was administered in pelleted diet, 1%, for the entire lifetime of the hamsters. While there were significant increases in the rates of adrenal cortical adenomas in male and female hamsters exposed to IR chrysotile compared to pooled control groups, they were no longer significant when contrasted to the temporal control groups. Additionally, the biologic importance of adrenal tumors in the absence of intestinal or mesothelial neoplasia is questionable. Combination studies using IR chrysotile and 1,2-dimethylhydrazine (DMH) were considered inadequate because of a lack of an increase in intestinal neoplasia in the DMH group.

Dr. Swenberg said that several aspects of the study conduct and reporting require attention prior to release of a final report. Information presented on missexed animals is unclear; figures 2 through 7 show large fluctuations in animal body weights with no explanation; information on the DMH experiment is incomplete, including whether DMH or DMH dihydrochloride was used. Also, he said, only scant information on non-tumor pathology is included and the report should be modified to include at least summary data; comment should be made concerning review of the clinical records for autolyzed or cannibalized animals. He said that on pp. 56-57, the report implies that some of the animals receiving amosite in a study by Ward received azoxymethane. This requires clarification.

As the secondary reviewer, Dr. Mirer said notice should be given in the report of the large variation in duration of exposure in the absence of terminal sacrifice, which differs from past or standard experimental design. He noted there were large differences in median fiber length for both SR and IR as measured by electron microscopy vs. light microscopy; this difference should be explained, and, further, should be related to the distribution of fiber sizes found in environmental diet samples. He reiterated the inadequacy of the DMH studies in that a literature report observed a much higher incidence of hemangiomas and hemangiosarcomas in DMH-treated hamsters than were seen in the current study. Dr. Mirer called for references in the conclusions to studies in hamsters of asbestos exposure by other routes of administration. He emphasized again that issues on the nature of the test material need to be resolved before the conclusions can be meaningful.

Dr. Williams suggested that the DMH studies may have been deficient because the DMH was not properly buffered to prevent decomposition of the DMH. He also supported Dr. Swenberg's request that the discussion on the Ward study be clarified. He asked that summary data be included from an EPA report showing various forms of asbestos to be inactive genetically. Dr. Mirer elaborated further on experiments not done which might have aided interpretation of the results. One had to do with uptake and translocation of asbestos fibers in the body, while the other related to whether asbestos pelleted in diet is available to be absorbed and/or translocated in the same way that asbestos suspended in drinking water would be.

Dr. Swenberg moved that the report on the bioassay of chrysotile asbestos be approved following minor revisions indicated. Dr. Mirer seconded the motion and it was approved unanimously.

3. Amosite Asbestos. Dr. Swenberg, as the primary reviewer, for the report on the bioassay of amosite asbestos, agreed with the conclusion that, under the conditions of the bioassay, the ingestion of amosite asbestos was not carcinogenic in male and female Syrian golden hamsters. The asbestos was administered at the rate of 1% in pelleted diet for the entire lifetime of the hamsters. He said that several of his comments on chrysotile asbestos also apply to this report, including improving the description of animal replacement following missexing, incorporating additional non-tumor pathology data and information on autolyzed or cannibalized animals, and rewriting the discussion section on the studies by Ward on azoxymethane.

As secondary reviewer, Dr. Mirer said that all of his comments on the chrysotile study applied to this study as well. He inquired as to the rationale for it being a life-time study as opposed to the usual terminal sacrifice. Dr. E. McConnell, NTP, said this was done to avoid missing late appearing tumors, e.g., inhalation studies with asbestos in rats by others have shown most mesotheliomas did not appear until after 27 months. Dr. Moore said there was disagreement between the original pathologist and the pathology working group for both this report and the chrysotile asbestos report. Dr. Swenberg felt this was handled well in the reports. He said the quality assurance review findings should also be included or at least a statement to the effect that the findings are available on request. Dr. Swenberg moved that the report on the bioassay of amosite asbestos be approved following minor revisions. Dr. Mirer seconded the motion and it was approved unanimously.