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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES
P.O. BOX 12233
RESEARCH TRIANGLE PARK, N.C. 27709
919/549-8411, Ext. 3201

Dr. Robert H. Mereness
Executive Director
Asbestos Information Association/North America
1660 L Street, N.W.
Washington, D. C. 20036

Dear Dr. Mereness:

Recent events indicate a need to assess the carcinogenicity of orally ingested asbestos or asbestiform minerals.

As Chairman of the DHEW Committee to Coordinate Toxicology and Related Programs, I asked Dr Raymond E. Shapiro, Food and Drug Administration, to head a Subcommittee on Asbestos Protocols. The purpose of this subcommittee was to review all existing data with respect to the biological effects of orally administered asbestos, with particular reference to carcinogenesis; and, if necessary, to develop appropriate protocols for studies to elaborate on any data deficiencies in this area. After reviewing the existing data the subcommittee developed a draft of a working document which is enclosed.

This subcommittee working draft is not intended to be a final protocol. Rather, it provides a basis for comment and discussion which will lead to the development of a protocol for studies. The subcommittee believes, however, that the working draft is far enough along that it is now appropriate to seek the comments and views of scientists working in this area, affected industries, and public interest groups. I invite your written comments on this working draft by February 14, 1975.

In addition, subcommittee members will be available on Tuesday, February 11, 1975, to discuss the working draft and answer any questions you may have. This discussion will begin at 10:00 a.m., Conference Room 8 of Building 31, (Sixth Floor - C Wing) on the NIH Campus. If you plan to attend the meeting, please notify my office as soon as possible so that we may be sure adequate meeting space is available.

Sincerely yours,

D. Rall

David P. Rall, M.D., Ph.D.
Director

Enclosure

WORKING DRAFT PROTOCOL

SUBCOMMITTEE ON ASBESTOS PROTOCOLS
DHEW Committee to Coordinate Toxicology and Related Programs

The Subcommittee on Asbestos Protocols determined that adequate data is not available for a determination of the carcinogenicity of orally administered asbestos. It considered many experimental approaches as to the best means for securing adequate data and reached the opinion that, as a minimum, a major chronic carcinogenicity study is warranted.

The current major study working draft reflects the Subcommittee's consideration and response to critiques received on its initial draft proposal. The current working draft consists of:

(1) Outline

(2) Written comments providing insight as to the background deliberations and rationale for the decisions (impasse) reached

(3) Comments relevant to the deliberations of the Subcommittee regarding a multispecies approach

(4) The Proposed Memorandum of Need developed by Dr. W. Horowitz, Food and Drug Administration, with respect to methods development for quantification of asbestos fibers was accepted by the Subcommittee. The work defined in this memorandum is now being conducted through an FDA contract

CHAIRMAN, SUBCOMMITTEE ON ASBESTOS
PROTOCOLS

OUTLINE OF THE WORKING DRAFT
OF THE ASBESTOS SUBCOMMITTEE'S MAJOR STUDY

Test Species - Rat

Test Strain - Inbred F344 or other (see comments)

Positive Control:

a) chemical producing gastrointestinal in rat strain chosen

b) one dose level

c) two groups exposed via food or water

Duration of Study:

a) life time (±36 mo.)

b) SPF condition

Fiber Type by Priority Rank:

a) Chrysotile

b) Crocidolite

c) Tremolite

d) Amosite

Fiber source - UICC preferred

Diet:

a) powdered

b) defined, constant formulation

c) control contaminants

Dose and Route

Food; high dose 1% (0.5gm/kg/day)
low dose (see comments)

Water: 10-20 ppm dependent upon suspension properties (see comments)

Number of Animals:

Control - 1000

Positive Control - 200 for food; 200 for water

Chrysotile:

Food - 2 doses, 550 each dose

Water - 550

Number of Animals: (Cont'd.)

Crocidolite:

Food - 2 doses, 550 each dose

Water - 550

Tremolite:

Food - 2 doses, 550 each dose

Amosite:

Food - 2 doses, 550 each dose

Water - 550

Another consideration was the postponement of the chronic study until a species more suitable for the model test system than the rat was found. These searches would be predicated upon demonstration of the penetration of asbestos fibers into and through the gut. Such penetration has been reported by South African workers for the baboon. While these studies are highly important and necessary in the long run, the Committee did not feel that the chronic carcinogenicity studies should be postponed while this data base was being developed. Even with the rat, such a chronic study would take 3 to 4 years to complete.

CHOICE OF STRAIN AND POSITIVE CONTROL

The problem in using an inbred vs. an outbred strain were discussed. Ideally, the F_1 generation resulting from the cross of two inbred strains would be the best test animal model since it allows genetic uniformity coupled with hybrid vigor. However, this may not be feasible in a study of this size. In addition, we might also lack the necessary background data with respect to this cross. Therefore, the Subcommittee recommends the use of an inbred strain.

The criteria for the choice of a specific strain for this proposed study is twofold: (1) a known high survival rate of control animals into the third year of life, and (2) a known low spontaneous tumor incidence. The key point is that whatever strain is chosen, it should not have an early proclivity to specific tumor type(s) which affect survival. Various strains were discussed and the Fisher 344 rat appears to be a suitable possible candidate.

SUBCOMMITTEE COMMENTS

Working Draft on Oral Asbestos Major Study

TEST SPECIES

The Subcommittee discussed the pros and cons of using rodents, for the testing of orally ingested asbestos for carcinogenicity. On the one hand, we had to consider the statements at the North Carolina Asbestos Conference that the rodent was a poor animal model for this purpose. In addition, several negative feeding studies have already been completed in this area. On the other hand, since these studies are, in the main, unpublished, one does not know if the negative results obtained were confirmation of the objections raised at North Carolina, or possible inadequacies in design and execution. In addition, alternative animal model systems that might be chosen, e.g., dog, minipig or non-human primate would require up to 7 years or longer before meaningful results might be obtained. Even with the potent liver carcinogen, aflatoxin, fed to non-human primates at high doses, it took 5 to 7 years for a hepatoma to develop. Therefore, in light of the charge to this Subcommittee it was concluded that a properly designed and executed ingestion study with asbestos should be undertaken with the rat to determine whether this model system does or does not respond to ingested asbestos.

The Subcommittee recognizes that while positive results will be immediately accepted, negative results may be interpreted as a choice of the wrong model system to test the question. In partial recognition of this situation, the Committee discussed a multispecies approach. However, until definitely proven otherwise, the Subcommittee feels that a major effort should be made along classical toxicological lines, i.e., a well designed rodent study.

The Committee concluded that in terms of whether or not ingested asbestos fibers may induce gastrointestinal cancers, the animal strain should have a demonstrable potential to develop such tumors when exposed to a chemical carcinogen. Therefore, the choice of the chemical for the positive control and the choice of strain are interrelated.

The only positive control of any real meaning is one producing G.I. tumors.

The emphasis on gastrointestinal cancers with respect to asbestos is predicated on the reported increase in these cancers in occupationally (inhalation) exposed workers. Since small amounts of asbestos may be ingested in food and fluids, the possible significance of these background exposures is of interest.

It is also recognized that while we may be interested mainly in the target organs, the gastrointestinal tract with respect to man, challenging any model animal system with the same agent does not mean the same response patterns will be seen in the animal model as is speculated for man.

Work at NCI has indicated that rats of the AxC strain develop gastrointestinal tumors when fed N,N'-2,7-fluorenylenebioacetamide (2,7-FAA). Choice of this strain, therefore, would meet the requirements stated above.

In addition to 2,7-FAA some other chemical carcinogens that warrant consideration are cycasin, nitrosoguanidine and nitrosourea.

The Committee felt that data should be sought on other strains that develop gastrointestinal tumors after ingestion exposure to chemical carcinogens. These might lead to possible alternatives.

The Subcommittee recommended that the question of strain and choice of positive control be discussed with Drs. Katherine Snell and Howard Steward of the NCI. A meeting was arranged by the Chairman with these two individuals on Wednesday, July 17, 1974. These discussions will continue.

On Monday, July 22, 1974, the Chairman contacted Dr. Sid Siegel of the NCI. Dr. Siegel has promised to search their files for a list of compounds eliciting a carcinogenic response in the G.I. tract, when administered orally, and where it was published. With this data base, from which we can also determine the species and strain used, the final choice of strain and positive control should be that much easier to make.

The use of 200 animals at one dose level is considered adequate for each route of administration.

DURATION OF STUDY

The study is to encompass the life of the test animals.

Given that a long latent period could precede neoplasia, survival through the second and into the third year of life is desired. The need for utilizing SPF rats, housed under SPF conditions, is an explicit recommendation.

DIET

The Subcommittee recommended the use of a nutrient defined, constant formula diet. This diet would be monitored for contaminants. If feasible, maximum contaminant levels will be set.

The question of mixing asbestos fiber and powdered chow together, then pelletizing, was discussed. The Subcommittee felt that the pressure and heat generated in palletization might alter the asbestos fiber.

The consensus of the group favored checking out the use of a powdered chow dispensing unit as now being used at NCTR. This unit apparently appreciably reduces the dust and inhalation hazard.

The possibility of mixing the asbestos fiber and chow with 3% corn oil was also discussed.

The Committee discussed the purity of the diet and the drinking water to be used. If a purified semisynthetic diet and pure water were used, a positive response in these studies might be interpreted as showing that asbestos, per se, is a carcinogen. On the other hand, if the diet and/or water contained trace amounts of chemical toxicants or carcinogens, a positive effect might have two possible interpretations: (1) asbestos is a carcinogen, per se, and/or (2) asbestos is a cocarcinogen. Since man lives in the "real world" the use of a defined (not purified semi-synthetic) diet and tap water should be used.

The use of a semisynthetic diet would be recommended for other studies when one might wish to carefully study possible interactions. When a semisynthetic diet is chosen, one would again have to search the literature for data on strains that will tolerate this particular diet.

DOSE AND ROUTE

The Committee recommends that asbestos be tested in food as well as water.

Human asbestos exposure estimates were determined several ways:

Estimates of Human Ingestion Exposure

1. Cunningham mass: 1×10^{-6} gm/liter

   70 kg man: drink two liters: 0.03×10^{-6} gm/kg/day plus cook liters: 0.06×10^{-6} gm/kg/day and if assume inhaled and completely swallowed an amount equivalent to the above:

   total ingested: 0.11×10^{-6} gm/kg/day.

2. Kay mass: 1×10^{-9} gm/liter (Ontario)

   drink 2 liter: 0.03×10^{-9} gm/kg/day plus cook 2 liters: 0.06×10^{-9} gm/kg/day plus equiv. swallowed air exposure:

   total ingested: 0.11×10^{-9} gm/kg/day.

3. Duluth: assume mass: 25µg/liter

   drink 2 liters: 0.7×10^{-6} gm/kg/day plus cook 2 liters: 1.4×10^{-6} gm/kg/day plus assume equivalent swallowed air exposure:

   total ingested: 2.8×10^{-6} gm/kg/day.

4. Range: 0.03×10^{-9} to 3×10^{-6} gm/kg/day

   a range of 5 orders of magnitude depending on assumptions

Fiber Size	Daily Permitted Occupational Exposure (gm)[1]	Assume Inhaled is all Swallowed (µg/kg/day[2])
10µ X 4µ X 4µ	16.25×10^{-3}	230
6µ X 2µ X 2µ	2×10^{-3}	29
(3µ X 1µ X 1µ)	$(0.25 \times 10^{-3}$	(4)
(1µ X 0.3 X 0.3µ)	$(7.5 \times 10^{-6}$	(0.1)

1. Air Standard: 5 fibers/cc (>5µ)
   Fiber S. G. = 3
   8 hours day
   Resp. air intake: $0.7 m^3$/hr.
2. 70 kg man

Diet Levels

The maximum dose in the diet was set at 1%. If we assume a 20 gm per day food intake by a 400 gm rat at 1% asbestos in the diet, we have an exposure of 0.5 gm/kg/day. This level ranges from 1.6×10^{-5} to 1.6×10^{10} time our projected level of possible human exposure. Since animal exposure is at least 160,000 times higher than projected human exposure, nothing is gained by raising this relationship another order of magnitude relative to the potential loss in adversely affecting animal health.

The use of such high levels in carcinogenicity testing of chemicals has raised the question by some of measuring the potential of an effect of alternate or aberrant metabolic pathways. However, in terms of asbestos fibers, one is possibly dealing with a physical or physical/chemical cellular interaction, non-metabolically related in terms of chemical degradation. In this case, the use of high doses of asbestos does not carry the same implicative objections associated with chemicals.

There were several recommendations that the study include the definition of a dose-response curve for each asbestos fiber type being tested in the food. Implicit in this recommendation is the assumption that a positive response is expected. This is precisely the question being asked; namely, is orally ingested asbestos carcinogenic. The Subcommittee feels that it is premature at this time to go to the expense of testing four dose levels of each asbestos fiber type in the food. With the number of animals involved per level of exposure, additional exposure levels within each fiber type would push the proposed study into even still larger cost figures. Therefore, in the working draft, the Subcommittee, in order to be able to cover all asbestos fiber types of interest, recommended two dose levels per asbestos fiber type in the food. We reaffirm this recommendation.

The question of what two doses to recommend was next considered. As discussed previously, 1% in the diet was agreed upon as the upper dose. Initial discussions recommended 0.01 or 0.001% in the diet as the second dose. The Subcommittee recognizes that this dose is too low.

Two alternatives then discussed were 0.5%, or 0.1%, in the diet. These discussions were predicated upon the assumption that the highest dose elicited a positive response. Those advocating 0.1% in the diet felt that if the response obtained at 1% was on a plateau of the dose-response curve, reducing the exposure by one-half may not be sufficient to produce a significant change in observed tumor incidence. If one was not on the plateau, one would still see a change in tumor incidence with reduction in dose by a factor of 10.

Those favoring 0.5% argued that if the tumor incidence at 1% asbestos in the diet were even as high as 50%, with a projected slope of one, a reduction of dose by a factor of 10 would give a tumor incidence of only 5%. This might not be significantly different from the background level to establish a second "effect" point. If the projected slope were greater than 1 or if the tumor incidence at 1% asbestos in the diet were much less than 50%, the possibility of obtaining a second "effect" point was still further reduced. Even with a projected shallow slope, this argument still holds true.

The discussion then resolved into which is of greater importance: establishing the second point as a possible "no-effect" level or determining two effect points. Since this study is designed as a carcinogenicity study, those advocating doses of 1 and 0.5% in the diet felt it was necessary to maximize the potential for obtaining two effect levels. Thus, if a positive response is obtained with two effect points, a better approach to a mathematical calculation of a possible permitted level of exposure may be made with two dose related effect points than just one. Proponents for choosing the second dose at 0.1% recognized this point, but felt it was of greater importance to define a possible no-effect point.

The Subcommittee was unable to reach unanimity on this point. Of those present at this time, Drs. Groth, Ligon, Munro, Shibko and Tardiff voted for the second dose at 0.1% in the diet, while Drs. Shapiro and Stanton voted for a second dose at 0.5% in the diet.

Another discussion with respect to doses of 1.0 and 0.5% in the diet centered upon possibility of dose overlap. Dose is a function of food consumption and variation in food consumption per day leads to dose variation. Also, any variation in food consumption per unit weight of animal leads to possible dose variations. If there is a 20% variation around the mean, then the doses we are then comparing are 0.5 gm/kg/day (range 0.4 to 0.6) vs. 0.25 gm/kg/day.(range 0.20 to 0.30). If one took 1/2 the log difference between 1 and 0.1, the antilog of 0.5 x 10 would give a dose of 0.3% in the diet. This would then result in a sharper

Food consumption records are, therefore, absolutely necessary and the total dose received should be calculated from the start to finish of the experiment.

Water Levels

If municipal water contains 25 ug/liter, an 80 fold increase in water content would give 2 ppm in the water. If one assumes that the rat food contains some fluid phase to reduce dust, let us then assume the 400 gm rat will drink 10 ml/day, or an exposure of 5 X 10 gm/kg/day. The three doses, two routes are now geometrically related.

A key point is how much fiber and at what size distribution will stay in suspension. Preliminary EPA studies (Dr. Tardiff) have indicated that up to 10 mg/liter (10 ppm) of chrysotile, crocidolite, and another amphibole may be suspended in water. This is primarily small material. Thus, the asbestos in water study appears to be feasible. However, it should be recognized that the particle size distribution to which the animal is orally exposed by placing asbestos in water is different from

that when asbestos is mixed into the diet. The actual particle size distribution in water should be accurately determined.

For the asbestos in water treatments, in order to minimize the effects of settling out of fibers, it was suggested that water bottles be prepared every afternoon and taken away in the morning.

Dietary preparation and waste disposal must be carefully standardized.

Air monitoring for fiber content should also be done every six months: at night as well as during the day when cages are being changed.

At each time of sacrifice, several fecal pellets should be saved from the cage holding that particular animal. These pellets should be analyzed to see whether the size distribution and chemistry of the asbestos fiber changed during passage through the G.I. tract.

The Committee considered and rejected the gavage route of administration for the following reasons: (1) possible bolus effect, (2) time and cost factors for the number of animals involved, (3) possible loss of animals during the period of treatment and (4) interactive irritation artifacts leading to cancer.

NUMBER OF ANIMALS

The number of animals chosen is based on a lifetime study, under SPF conditions where a significant number of animals will survive into the third year of life. If one expected a 50% survival into the third year, starting with 500 animals (250 M, 250 F), would only give 250 animals on

which to base a conclusion. One assumes, in this case, the possibility of no effect being seen the first two years and any possible effects that may occur in the third year occurring at a low incidence. Therefore, the Committee recommended 500 animals for each treatment level.

The Subcommittee also recognizes that it is never possible, in the real world, to have a sufficient number of animals per treatment group to reduce the possibility of a false negative to a mathematical near zero level. We do feel that the number of animals chosen is adequate, particularly when one considers the large number of questions we are attempting to answer at the same time.

The numbers chosen are a compromise based upon feasibility of carrying out the total study as well as the assumption that possible target organs, particularly the gastrointestinal tract, will have a low noise level. The more accurate the determination of background noise, the better one may be able to measure possible treatment differences. Therefore, the Committee recommended that 1000 animals (500 M, 500 F) be established as a control group.

The Subcommittee recommends that an additional 50 animals be added to each treatment group in the major rat study. In this way, 10 animals may be sacrificed at 6, 12, 18, 24 and 30 months. With this serial sacrifice, we have a samll pathogenicity study as well as time frame reference for tissue fiber content. McCrone Associates will analyze 7 tissues, from one animal, for asbestos content, at a cost of of $200.

FIBER TYPE

The Committee ranked fiber type as to priority in oral carcinogen testing. In order of decreasing priority they are: chrysotile, crocidolite, tremolite and amosite. The priority ordering is based on the total number of the population that may be exposed.

Chrysotile exposure may occur in fluids due to the use of chrysotile containing filters for certain beverages, the possibility of abrasion from chrysotile containing asbestos-concrete water conducting pipe, and from the geological contribution to water that may be used for drinking. Solid phase ingestion of asbestos may occur from possible chrysotile contamination of talc used in foods and orally ingested drugs.

Therefore, chrysotile should be tested in food as well as in water.

It was recently reported that crocidolite was used in asbestos-concrete water conducting pipe. If abrasion of fibers from this pipe occurs, crocidolite would then appear in the water and could also be contained in foods prepared from this water.

Therefore, crocidolite should be tested in food as well as in water.

It should be noted that placing the amphibole crocidolite in the second priority ranking, we recognize that the level of exposure is possibly much lower than for amosite but the number of people potentially exposed in the former case is inordinately larger than the latter. Furthermore, if the asbestos question is only a subset of the more general fiber question, the choice of several fiber types within the subset may give

a clue as to whether any possible response is physical or physical/chemical in nature. Therefore, the Committee strongly recommends that all fiber types be considered simultaneously in the major chronic feeing study.

Tremolite is the major possible asbestos contaminatnt of talc used in food and in orally ingested drugs.

Therefore, tremolite need only be tested in food.

Since talc contains anthophyllite and chrysotile, as well as tremolite, the Subcommittee recommended that consideration be given to feeding a mixture of the three in proportion to their occurrence as a contaminant in talc.

Amosite exposure is a case of a localized situation rather than a national one; namely, the problem at the western end of Lake Superior. The question is one of amosite in the water which could also be contained in foods prepared from this water.

Therefore, amosite should be tested in food as well as in water.

FIBER SOURCE AND QUANTITY

The Subcommittee agreed that the U.I.C.C. standard asbestos fibers should be used whenever possible. It was recommended that U.I.C.C. Chrysotile B be chosen, a mixture of chrysotile from 8 mines in Canada.

In addition, U.I.C.C. crocidolite and amosite would also be used. Dr. Groth mentioned that the only commercial deposit of tremolite was in Northern Italy. He had obtained a small sample of this material from

John S. Manville. The Chairman has already written Johns-Manville about obtaining a sufficient quantity of this tremolite material to conduct our proposed feeding study. The Chairman has been formally notified that U.I.C.C. material would be available for our purposes.

The Subcommittee recommended that all asbestos fiber types used be carefully characterized as to fibers within each size category, and a distribution by weight.

The protocol recommends, at the highest level, 1% in the diet. This is 0.2 gm/rat/day. For 1000 days this would be 200 gm/rat and for 500 rats the total amount of asbestos fiber needed would be 100 kg. A level of 0.01% in the diet would only take a total of 1 kg for the same number of animals. The water intake study would be still lower.

If one considers a factor of 50% to 100% as a loss factor in preparing diets, spillage, waste, etc., the fiber needs are therefore from 150 to 200 kg per asbestos type.

In the consideration of smaller scale studies with other species in the multispecies approach, additional amounts of fiber will be needed.

In addition, if other laboratories, possibly in other countries, want to undertake studies on other facets of the asbestos question, again additional quantities of fiber will be needed to have a common baseline for comparison.

Finally, if any one fiber type should give positive results in any of the proposed studies, a sufficient amount of material should be on hand to be able to conduct further investigations.

Considering all these factors, the Committee felt that it was reasonable to start out with 1 ton of each material. These samples should be well characterized and contain a complete spectrum of fiber sizes.

The logistics implied in the above are enormous. One might approach industry to solve this problem, but this approach would be criticized in some quarters. On the other hand, the UICC Committee which prepared the previous set of International Standards are an alternative source. They have had past experience in handling quantities of material of this size and in these characterizations. The solution to and successful operation of this aspect of the protocol is the key to everything else.

Miscellaneous Factors

A pathology protocol at sacrifice must be developed with particular attention paid to the means of examining the G.I. tract.

Asbestos in the food and waste contaminent in the cage must be so handled that there is not a confounding inhalation exposure to the test animals. In addition, occupational health aspects of all people associated with all phases of the animal study must be carefully controlled relative to safety.

Waste disposal must be such, with the quantities of asbestos involved, that there is no environmental aspect.

The question was discussed of randomization of animals and the potential for cross contamination when all treatments are in the same room. It was felt that due to the known carcinogenicity of the positive control, these animals should definitely be kept in a separate room. Perhaps, the asbestos levels and controls should be separated.

The Subcommittee recommends that this question be aired with the [illegible].

There should be strict guidelines for animal observations during the course of the experiment.

SUBCOMMITTEE COMMENTS

Multispecies Approach

Only to involve chrysotile and crocidolite in diet at dose of 0.5 gm/kg/day.

Marmoset

At the San Antonio meeting, November 1973, of Dr. Saffiotti's contract carcinogenesis program, a report was given of spontaneous intestinal tumors in the Oak Ridge marmoset colony. Depending upon the possible availability of animals, chrysotile and crocidolite, 0.5 gm/kg/day, should be tested on up to 50 animals for each fiber type-food exposure.

Considering the time needed for any possible positive results, this or any other possible non-human primate study should be initiated as early as may be practically managed.

Hamster

Colonic cancers have been produced by chemical agents in certain strains of hamsters. These strains, when identified should be challenged with chrysotile and crocidolite, at a dose of 0.5 gm/kg/day, 100 animals for each fiber type, 100 animals for the control, food exposure.

Mastomys

The mastomys, a South African rodent, shows many spontaneous tumors. From our point of view, the tumors of interest are carcinoids of the glandular stomach and adenomatous polyps in the area of the ileocecal junction.

Putting asbestos in the food, at a dose of 0.5 gm/kg/day, might exhibit a possible effect by either shortening induction time and/or increasing incidence. Chyrsotile and crocidolite will be tested, 100 animals for each fiber type, and 100 for controls.

Chickens

The chicken, upon administration of asbestos intratracheally, has developed tumors, indicating a susceptibility to asbestos. In addition, unlike the rodent, a pellet former, the chicken has a continuous flow GI tract. Chrysotile and crocidolite will be tested, 100 animals for each fiber type and 100 for controls, at a dose rate, in the food, of 0.5 gm/kg/day.

Trout

Recently, the trout has been shown to be a very sensitive system indicating a carcinogenic response from a variety of chemicals. The Committee recommended that both chrysotile and crocidolite be tested, in the food, in this model system and possibly in water as well.

SUBJECT: PROPOSED INVESTIGATION OF FDA -- The Isolation, Identification, and Determination of Asbestos

a. Statement of Work:

The purpose of this investigation is to develop a practical, reliable method for the isolation, identification, and determination of asbestos in foods, drugs, cosmetics, consumer products and tissues. Techniques must be developed to isolate the asbestos (where necessary) as used in these industries from such diverse substrates as mineral solids (e.g., talc, filters, building materials, food solids (e.g., rice, coating materials, food-packaging materials), semisolids (e.g., mayonnaise), and liquids (e.g., water, alcoholic beverages, filtered beverages, parenteral solutions). Solubilization, filtration, centrifugation, and flotation have been used for this purpose. Alternatively, direct measurement techniques may be developed (e.g., X-ray diffraction) and utilized where appropriate, or a combination of techniques. Novel techniques such as electrophoresis, previously unexplored for this problem, may be pursued. The method must contain provision for estimating particle size distribution.

To be practical, the method must require substantially less time for the analysis than the present 6 to 8 hours per sample required by electron microscopy but without sacrificing reliability with respect to identification. Computer interpretation of electron or optical images is a possible procedure.

To be reliable, the method must permit positive identification on identical samples by at least six laboratories on 10 samples with no false positive identification and not more than 1 false negative identification per laboratory. A lesser degree of reliability may be accepted with some type of products. The development program should attempt to obtain reproducibility in the same laboratory on the same sample within a factor of ± 4 (e.g., results should fall within 0.25 to 4 X 10^6 fibers/unit volume).

In the development of the method consideration also should be given to isolation, identification, and determination of asbestos after contact with foods and drugs for normal handling, storage, and distribution times encountered in commercial and consumer channels; and in contact with body fluids and tissues as would be encountered in long-term animal feeding studies.

The contractor must be aware that a laboratory environment often contains unsuspected sources of potential asbestos contamination. Adequate "clean-room" facilities is an essential requirement for the execution of this contract.

b. Funding

Estimated cost is of the order of $100,000 per year for two years. The possibility exists of conducting this project as a joint effort with the Environmental Protection Agency, Consumer Products Safety Commission, and other agencies. Since there is no way a contractor can assure success in meeting the requirements, this project will of necessity have to be conducted on a "best effort" basis as determined by the Project Advisory Group.

Equipment and facilities are not to be added to the cost of the contract. Contractor or his subcontractors must have adequate equipment and facilities prior to the submission of a proposal.

c. Prospective Contractors

IIT Research Institute
10 West 35th Street
Chicago, IL 60616

Battelle Institute
Columbus, Ohio

McCrone Associates
Chicago, IL

California School of Public Health
Berkeley, CA

Materials Research Laboratories
Penn State University
State College, PA

National Bureau of Standards
Washington, DC

d. Procurement Planning

1. Proposed Schedule for Performance and Critical Milestones

i Literature review of available methods and survey of asbestos uses in the food, drug, cosmetics and consumer products industries, including suppliers to these industries (purification techniques, weaving, packaging, etc.) and preparation of report.

ii (a) Set up and familiarization with various techniques which may be applicable to the solution of the problem.

(b) Testing various asbestos isolation techniques on a macro scale using optical microscopy.

(c) Preparation of authentic samples for comparison and storage experiments

iii Comparison of the various techniques on model systems

iv Application of the better techniques to practical samples

v Refinement of techniques based on the results of analysis of practical samples.

vi (a) Training of other laboratories in the procedures

(b) Conducting an interlaboratory trial of the developed methods(s).

(c) Final refinement of the method based on applications by other laboratories.

vii (a) Assistance in development of compliance program

(b) Preparation of final report

2. Contemplated Extensions or Desired Options

Asbestos is a relatively inert, unreactive material occurring in a number of different forms. The technical problem is very difficult and may require more time than estimated; on the other hand, the large scale support by EPA may develop solutions earlier than expected. If currently unknown applications of asbestos are encountered which introduce new problems, additional time will have to be allotted. If asbestos contamination can be eliminated or controlled by inspections, regulation, auditing, or other non-laboratory procedures, work on these types of controllable commodities may be eliminated.

3. Technical Monitoring

The Project Officer and/or the Project Advisory Group will meet with the contractor at bimonthly intervals. At least two of these meetings will be site visits. Reports must be submitted at least quarterly or as specific phases are completed. A final report is to be delivered 24 months after initiation.

4. Evaluation Criteria

The submissions will be assessed as follows:

a.	Experience of principal investigators	50
b.	Availability of facilities and instruments	25
c.	Evidence of understanding the requirements	10
d.	Suggestive ability to improve and develop new procedures	10

LIST OF INVITEES

MEETING TO DISCUSS WORKING DRAFT ASBESTOS PROTOCOL

February 11, 1975

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c. Suggestive ability to supervise subcontractor(s) and/or support personnel 5

e. Release of Information

Until the issuance of final regulations on the subject of asbestos in foods, drugs, cosmetics, and consumer products, information can be released only with the approval of the Project Officer.

Revised 1/2/74; W. Norwitz

WNorwitz:rlw
1/4/74

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