Weyzen

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L. Joe Deal, ADFO/OES

TRIP REPORT - PUBLIC MEETING OF AN EXPERT COMMITTEE CONVENED BY MR. CALIFANO TO EVALUATE THE STUDIES ON WHICH THE PROPOSED OSHA BERYLLIUM STANDARD ARE BASED; ATLANTA, GEORGIA; OCTOBER 9, 1978

In a recent memo to Mr. Califano, Dr. James Schlesinger noted the questions raised by the Scientific Community regarding the studies upon which the decision by NIOSH and OSHA to regard beryllium as a carcinogen were based. In a subsequent letter to Mr. Marshall (Enclosure 1), Mr. Califano announced that he had appointed a committee of independent experts to review these studies and report to him within a period of one month. This October 9 meeting of this committee at the Center for Disease Control (CDC) in Atlanta will be the only time that this group will physically convene.

The seven beryllium review consultants (Enclosure 2) met to consider the agenda shown in Enclosure 3. Several days previously each consultant had received a packet of material consisting of reports of 33 experimental animal studies; 7 reports of human studies, and 10 background references (Enclosure 4).

Dr. Foege, Director of CDC, described the ground rules for their deliberations: they are considered individual consultants who have been brought together to save time; each will provide an individual judgment on the following three questions; CDC will take their answers and prepare a report which will be sent to Mr. Califano by October 20, 1978:

1. Does beryllium cause cancer in at least two species of animals?

2. Is the beryllium - copper alloy a carcinogen?

3. Is there evidence that beryllium is carcinogenic to man?

The moderator, Dr. Millar of CDC, called for a discussion of the 33 animal studies (refer to the list in Enclosure 4). Each of six of the consultants reviewed 5-7 studies, then one prearranged person commented on the review. Below are the capsulized comments on each of the animal studies.

Pettigrew - E-1, E-2, and E-3 -- all three are intravenous studies in rabbits; all had insufficient controls so their validity rested on the assumption the osteosarcoma is a rare disease; Dr. Pettigrew was willing to accept the author's conclusions that cancers had resulted from these i.v. injections.

E-15 -- not reviewed because it dealt only with nickel sulfate; it was on the list only because E-33 refers to it.

E-10 -- only an abstract; very little data.

Dr. Kleinerman chipped in with the comment that it was unheard of to have spontaneous osteosarcoma in rabbits.

Milham - E-5 -- not applicable; study was on thorotrasts.

E-4 -- four out of five animals developed malignant bone tumors.

E-7 -- BeO, ZnO and SiO_2 were injected three times per week; the beryllium "caused" osteosarcoma (Milham agrees with the conclusion).

E-8 -- in this 1951 study, the experimentors were trying to induce beryllium disease - one rabbit got osteogenic sarcoma.

E-9 -- conclusion of this early study, i.v. beryllium injection resulted in neoplasm in rabbits.

Kleinerman - These six studies all involved inhalation of various beryllium salts with the lung as the target. These studies were not written in the classic style - actually written almost anecdotally.

E-17 -- inhalation of the oxide, sulfate, and fluoride (no metal or alloys); tumors do occur in rats - especially later after cessation of inhalation; 1-1½ years after cessation 44%-55% of the rats have carcinoma; poor controls; study includes five generations of tumor transplants.

E-18 -- more details of the inhalation schema; two strains of rats; beautiful graphs, but no confidence intervals.

E-27 -- using the sulfate; good evidence that cancer results; varies with the strain of rats.

E-28 -- contributes little; sulfate inhalation; also inhalation of alkaline phosphotase.

E-26 -- documents osteosarcoma in rabbits; contributes little.

E-33 -- never been published in a referred journal; contains a reference to Be alloys; no cancer in 33 animals exposed to Be -Cu alloys; cancer found in those exposed to BeO.

Falk - E-19 -- fluoride is active carcinogen; oxide is active in the rat; the sulfate is active in the rabbit. Using beryllium fluoride, the author gets a semblance of a dose - response curve. (2%, 4%, and 8% at 6, 12, 15 months - end point, lung cancer.)

E-20 -- exposure of monkeys to fluoride, sulfate, and phosphate (with low beryllium content) - no cancers, probably because of high toxicity of the salts.

E-21 -- complicated - rats exposed intertracheally to 25 mg of calcined BeO and sacrificed at intervals from one week to 1½ years; incidence of cancer reduced as the calcining temperature was increased (500°; 1100°, and 1600°).

E-22 -- a follow-on report to E-21; the exhaust was carcinogenic.

E-29 and E-30 -- a monograph; pulmonary cancer found in rats after exposure to the sulfate; 80 tumors formed in 53 rats (one rat was reported to have 17 primary tumors); exposure to monkeys - cancer induction takes 4-5 years; five cancers were found - in three different routes: inhalation, injection, and insufflation.

Discher - E-31 -- used three species (monkey, rat, and hamster) and two ores (beryl and bertrandite); exposure by inhalation; beryl produced tumors at concentrations of 15 mg/m^3; 9 out of 19 rats had adenocarcinomas; 4 out of 19 rats had epidermoid carcinoma. 0 out of 19 rats exposed to 5 mg/m^3 of bertraudite had tumors; no monkeys had tumors; hamsters had no cancers but unspecified "preliminary pathology."

E-11 -- doesn't add much new.

E-12 -- pathogenisis is interesting.

E-13 -- a worthless paper; poorly documented.

E-23 -- poorly documented; but the report does pull things together.

Matanoski - E-16 -- inhalation exposure of rats to 35 µgm/m^3 and sacrificed over time; of 300 rats 38% produced tumors; 67% of those that lived over nine months produced tumors.

E-25 -- 12 rabbits injected with zinc beryllium silicate in the tibia; 4 developed tumors in 12-15 months (4 died before 12 months).

E-30 -- monkey exposed by inhalation route; it was hard to tell the latency period because, if the monkey lived a certain period (two years?), the exposure was restarted; the first tumor appeared after six years (2000 hours of exposure); there were multiple primary tumors.

E-32 -- injection of rabbits with 1% soln. of BeO into the lower end of bone; after one injection there was no cancer after an early sacrifice (35 days) although there was precancerous lesions; of 42 rabbits sacrificed from 56-638 days after similar injection there were 24 with cancer; no mention is made of controls.

The seven papers written about human studies were all reviewed by Dr. Shy.

H-1 - H-4 -- These are successive revisions of a paper given at the OSHA hearings. McMahon had given H-1 a rigorous analysis. The CDC panel had recently reviewed the first three of these papers, resulting in the fourth draft. Because of the successive corrections, Dr. Shy's review is basically of H-4. I obtained a copy of his comments (Enclosure 5) so there is no need for recommenting his conclusions here.

Dr. Discher thought that more could have been said about the magnitude of these factors:

- use of regional cancer data;
- loss of many subjects to follow-up;
- the effect of military service;
- the failure to locate death certificates;
- the "healthy worker" effect (however, someone pointed also to the uncertainties introduced by the "turnover worker" effect; i.e., those many people during the '40's who worked for a very short time (weeks or very few months)); and,
- the smoking question.

There was a great deal of discussion - pro and con - re the fact that most of the excess cancers (over expected) came from that part of the population that had worked at the Reading plant for a period of less than one year. Why should this be? A number of suggestions, some of them contradictory, were offered by the consultants.

Dr. Discher cautioned that the tendency is to make more of this paper than is warranted. It has definite limitations. Furthermore, it has not been published in a refereed journal so all evaluation (and nit-picking) is being compressed into a short, few months period. Actually, this paper represented good epidemiology.

H-5 - H-6 -- These were two studies with slightly different populations; H-5 is a study of 3,685 beryllium plant workers between 1938 - 1948; their controls are the workers in a viscose rayon plant. H-6 is a study of beryllium plant workers during the period 1942 - 1948; for controls, the Ohio lung cancer rates were used. In one significant summary table, 11 of the 12 cells exceeded the cancer rates for the rayon plant workers (H-5). In 9 of 12 cells, the cancer rates exceeded the rates for the State of Ohio (H-6). The excess cancer was not limited to the < one year employment group (the data were not corrected for age).

Mr. Shy's conclusion was that these studies lacked certain essential features; that they were more a descriptive association; but, in point of fact, they cannot be easily explained away.

H-7 -- This study was conducted with the population of the Beryllium Disease Registry; 421 cases, using as a comparison the 1965 - 1967 U.S. lung cancer rates; seven cases of lung cancer were found (compared to 3.4 expected); virtually all of these cases (six out of seven) were in the acute beryllium group; five out of the seven had worked in the beryllium plant for < one year. Dr. Shy pointed out certain deficiencies:

- the statement that the excess lung cancers was not do to smoking was only a hypothesis, no proof was offered;
- the study does not confirm or reject the hypothesis that beryllium causes cancer;
- there is an association, but there are also alternate explanations;
- the population should be compared with other pneumonoconiosis registries; and,
- once a case is identified and added to the registry, it has an altered medical regimen.

Following the reviews and discussions of the 40 papers, the seven people who had signed up to speak (as members of the public) were allotted 10 minutes apiece to do so. They were:

Mancuso - (author of H-5 - H-6) answered a number of questions that had arisen during the discussion.

Ms. Seminario - an industrial hygienist for the AFL-CIO in Washington commented on the selection of materials that were provided the consultants. She thought that they should have been given:

- the responses of Wagoner, Infante, and Bayliss to the CDC panel's questions;
- the updated NIOSH criteria document;
- the early human studies of Mancuso, Hardy, Bayliss, and Kazemi; and,
- the critique of the Wagoner, et al. study prepared by Dr. Lloyd under contract to the Steelworkers Union.

Groth - a pathologist researcher, answered several questions about his work.

Powers - v.p. of Brush-Wellman Company distributed Dr. Rogers paper, McMahon's most recent critique and copies of the B-W testimony before the OSHA hearing. He also pointed out that 70-80% of the workers exposed to beryllium are exposed only to the beryllium - copper alloys. (These alloys include a high strength alloy - 1.6-1.85% beryllium and a high conductivity alloy - 0.4-0.6% beryllium.)

Infante - one of the NIOSH workers, answered questions regarding the human studies he conducted.

Lloyd - biometrician with OSHA, pointed out the weakness of the consultants lacking the historical perspective regarding this problem.

Wagoner - NIOSH researcher, now loaned to OSHA, fluently answered panel questions regarding his rather controversial study.

There followed an intra-consultant discussion, part of which was open to the public and part of which was closed. The Chairman, Dr. Millar, said that he would like to have a one paragraph answer to each of the three questions before they left Atlanta (although they would be allowed to add or amend their answers anytime before COB Friday, October 13).

Here are my opinions and speculations:

1. This was a very competent, hard working and fair group of consultants. One of them adhered only to thoughts or concepts which supported a conclusion of carcinogenicity but all of the others addressed themselves to both sides of the question equally.

2. Even though the time was short and the amount of material to assimilate was voluminous, it cannot be said that Dr. Schlesinger's question of beryllium carcinogenicity did not receive a thorough, fair assessment.

3. Although Dr. Shy expressed an opinion on the results of the deliberations to the press later in the evening (it appeared in the Washington Post on October 10, 1978), there can be only speculation as to the answers to the three questions which CDC will transmit to Mr. Califano. My speculations are:

   a. Beryllium will be considered a carcinogen for rats, rabbits, and monkeys, thus fulfilling requirements for basing OSHA beryllium standards on its carcinogenicity.

   b. There is no evidence one way or other on the carcinogenicity of copper - beryllium alloys, thus throwing it back in NIOSH - OSHA laps to decide to include it in its proposed standard because, ater all, beryllium is involved, or exclude it on the basis that there is no evidence that the Be-Cu alloy is carcinogenic (my guess is that they would take the former action).

   c. There is an association between human exposure to beryllium and lung cancer, but it is not a strong one and does not have the unequivocal nature that one would like to see. I think it will be good enough for OSHA.

Donald M. Ross

Donald M. Ross, Chief
OS&H/OES

Enclosures:
As stated

cc: H. Hollister, DIR/OES
SA Branch