MIR
MALLINCKRODT
INSTITUTE OF RADIOLOGY
WASHINGTON UNIVERSITY
MEDICAL CENTER

DIVISION OF
NUCLEAR MEDICINE

4 September 1996

James P. Dwyer
Division of Radiation Safety and Safeguards
U.S. Nuclear Regulatory Commission
Region I
475 Allendale Road
King of Prussia, PA 19406-1415

Re: Report of Medical Consultant to Augmented Inspection Team
Internal P-32 Contamination of Researcher at National Institutes of Health (NIH)
Docket No. 030-01786; License No. 19-00296-10; Event No. 29008

Dear Mr. Dwyer:

The following Medical Consultant's report is provided in response to the letter from Jenny M. Johansen dated 5 July 1995 . In preparing this report, I have had access to several different sources of data and information. These included (1) numerous telephone conversations and electronic mail communications with you, as well as conversations with Donna Beth Howe (NMSS) and other members of NRC staff, on multiple occasions since I was first contacted by Larry W. Camper on 30 June 1995; (2) a telephone conversation with Shen-sho Tseng, M.D., the contaminated researcher's private physician on 21 July 1995; (3) telephone conversations with Shawn W. Googins, CHP, of the NIH Radiation Safety Branch on 23 July and 3 November 1995; (4) telephone conversations with James Schmitt, M.D., of Occupational Medical Services at NIH on 26 July, 15 August, and 1 November 1995; and (5) telephone conversations with David Hickman, Ph.D of the Special Projects Division at Lawrence Livermore National Laboratory (LLNL) on 3 and 16 November 1995. I have also reviewed various documents including (1) an event chronology prepared by James Dwyer; (2) an 11 July 1995 summary of whole-body scanning date prepared by Jorge A. Carrasquillo, M.D., Acting Chief of the NIH Nuclear Medicine Department; (3) summaries of background information on phosphate metabolism and of studies to determine the chemical identity of the ingested P-32 (provided to me by Shawn Googins); (4) a letter dated 8 November 1995 to Shawn Googins from Ronald F. Goans, M.D., Ph.D. of the Radiation Emergency Assistance Center/Training Site (REAC/TS) at the Oak Ridge Institute for Science and Education (ORISE); (5) several August 1995 dosimetry estimate summaries and a supplement dated 17 October 1995 prepared by Michael Stabin, CHP, of the Radiation Internal Dose Information Center (RIDIC) at ORISE; (6) the dosimetry estimate summaries dated 26 October and 10 November 1995 prepared by staff of the Special Projects Division at LLNL; (7) copies of the contaminated researcher's medical records (consisting almost entirely of laboratory data) provided to the NRC by her attorney on 22 April 1996; and (8) a copy of a letter from a consultant, David A. Dooley, Ph.D., dated 15 April 1996 to the contaminated researcher's attorney, sent to me by the NRC on 27 April 1996.

Despite the fact that I have had access to a substantial amount of information as indicated above, I believe it is important for me to indicate that the useful medical information available to me in this case is actually quite limited. Selected medical information has been obtained

510 South Kingshighway Boulevard
St. Louis, Missouri 63110-1076
(314) 362-2809 FAX (314) 362-2806

through various telephone conversations and from the medical records supplied. However, the information pertaining to any symptoms or signs of illness that the contaminated researcher may have experienced before or after the presumed date of exposure is quite sketchy. I have essentially no information (other than laboratory records and the delivery record) concerning the researcher's medical condition since late July/early August. As you are aware, I have not had an opportunity to interview or examine the contaminated researcher directly.

Relevant Medical History and Medical Aspects of Event: The researcher is a 32-year-old Chinese woman, who reportedly had been in good health prior to the event. She underwent pre-employment evaluation at the NIH Occupational Medical Services on 14 September 1994. Her evaluation at that time was reportedly normal. At the time of the internal contamination event, the individual was approximately 17 weeks pregnant (this is presumed to represent the post-menstrual age of the pregnancy based on the recorded date of her last menstrual period of 1 March 1995 and her delivery of a full-term infant on 1 December 1995). Her pregnancy was undeclared. She reportedly had complained of "morning sickness" during the first three months of her pregnancy, but these symptoms had subsided during the first few weeks of June. Hemoglobin and hematocrit obtained on 12 June 1995 were 11.6 g/dL and 35.1%, respectively. This borderline "anemia" is a common finding in pregnancy, and is largely dilutional in most cases, as a result of plasma volume expansion. Her white blood cell count on that date was 7,660/μL and her platelet count was 249,000/μL, both values within normal limits. Her white blood cell differential count was essentially normal (78.5% neutrophils, 14.1% lymphocytes, 5.4% monocytes, 0.4% eosinophils, 0.4% basophils, and 1.2% atypical lymphocytes).

The investigation performed by the Radiation Safety Branch at NIH and by the NRC suggests that the internal contamination with P-32 occurred midday on 28 June 1995. The researcher reportedly developed right-sided back pain on that day or the next (the information available to me is unclear regarding this point). The researcher apparently reported this symptom to her private physician, but also indicated that the symptom was relieved by wrapping a towel around her abdomen, thereby suggesting to her physician that the discomfort was musculoskeletal in origin. Additionally, recurrent nausea and vomiting also apparently developed on either 28 or 29 June, and may have persisted for several days thereafter.

When the internal contamination was discovered on the evening of 29 June 1995, the researcher was seen in the Emergency Room at Holy Cross Hospital. Staff of the Radiation Safety Branch at NIH had contacted the Radiation Emergency Assistance Center/Training Site (REAC/TS). The REAC/TS physician spoke with the emergency room physician at Holy Cross Hospital and recommended hydration and administration of stable phosphate as treatment to maximize excretion of P-32. Hydration was performed, but the physician at Holy Cross Hospital elected not to administer phosphate.

Occupational Medical Services at NIH obtained a blood sample for assessment of the researcher's hematological profile on 30 June 1995. At that time, her hemoglobin and hematocrit were 10.7 g/dL and 31.3%, respectively. These values were mildly decreased by comparison with the measurements made on 12 June. The results, however, were still within the expected range for dilutional "anemia" of pregnancy. The fluids administered on the previous evening to hydrate the researcher may also have contributed to this result. Her white blood cell count was 7,300/μL and her platelet count was 230,000/μL. These results are normal. The white blood cell differential count remained essentially normal (79% neutrophils, 13% lymphocytes, 7% monocytes, and 1% eosinophils).

Only minimal subsequent medical history is available. The researcher apparently continued to experience episodes of vomiting, but the severity, frequency, and duration of these symptoms are unclear. The patient's private physician obtained additional laboratory data on 22 July 1995. At that time, her hematological profile was essentially unchanged by comparison with that on 30 June 1995 (hemoglobin 10.5 g/dL; hematocrit 31.6%; white blood cell count 6,710/μL; platelet count 223,000/μL; 76.4% neutrophils, 15.5% lymphocytes, 6.1% monocytes; 0.4% eosinophils, 0.4% basophils, and 1.3% atypical lymphocytes). Serum electrolytes were normal (potassium 3.6 meq/L; sodium 137 meq/L; and chloride 105 meq/L). Her total serum protein and serum albumin were both mildly depressed at 5.5 g/L and 3.4 g/L, respectively (normal ranges 6.3-8.4 g/L and 3.3-5.3 g/L, respectively). Additionally, her blood urea nitrogen (5 mg/dL), serum creatinine (0.4 mg/dL), and uric acid (1.8 mg/dL) were all below the normal range. I interpret these findings to be most consistent with plasma volume expansion during pregnancy. There was mild elevation of the serum aspartate aminotransferase (SGOT) concentration at 40 U/L (normal range 0-39 U/L) and of the alanine aminotransferase (SGPT) at 82 U/L (normal range 0-53 U/L). Elevations in the levels of these enzymes most often indicate hepatocellular injury, but can be seen with many different disorders involving many different organs and tissues. In the absence of other medical historical information and follow-up laboratory data, I am unable to determine the clinical significance of these enzyme abnormalities. The remainder of her chemistry profile on this date was normal.

Additional blood laboratory studies were performed on 5 August 1995. Her mild anemia remained unchanged and her SGOT and SGPT levels had returned to normal. Her white blood cell count was still normal, but the differential count showed a slight left shift (75% neutrophils and 7% bands), a finding of uncertain significance.

In a telephone conversation on 15 August 1995, Dr. Schmitt at NIH Occupational Medical Services reported to me that the researcher had declined to have further contact with the physicians at Occupational Medical Services. Dr. Schmitt further reported that he had spoken to the researcher's private physician who indicated that the researcher claimed to have persistent severe nausea and vomiting. Dr. Schmitt asked the private physician to contact me directly if he were willing to do so, but I never received a call from him.

Additional blood laboratory studies on 30 August 1995 were essentially unchanged, except for mild hyperglycemia (glucose 118 mg/dL). Fetal ultrasonography on 1 September 1995 was normal, and the measurements indicated a postmenstrual fetal age of about 27 weeks (which indicates a postmenstrual fetal age of about 18 weeks on 28 June 1996). Repeat hematological profile on 13 September 1995 again showed mild anemia (hemoglobin 10.6 g/dL) and 7% bands, and another on 11 November 1995 still showed mild anemia (hemoglobin 11.0 g/dL); with a normal white blood cell differential count.

The researcher was admitted in labor to the Columbia Hospital for Women Medical Center on 30 November 1995 and uneventfully delivered a grossly normal male infant on 1 December 1995. The infant's Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. Newspaper accounts stated that the baby was apparently healthy.

I have had access to no subsequent medical information concerning the researcher. In a telephone conversation with Dr. Schmitt on 1 November 1995, I confirmed that he had had no follow-up contact with the researcher since he and I had last spoken on 15 August 1995.

Based on the medical information available to me, I am unable to determine whether any of the reported symptoms experienced by the researcher are related to ingestion of P-32. However, as noted below, it is highly unlikely that these symptoms are radiation related. Since the chemical form of the ingested P-32 remains uncertain, chemical toxicity cannot be entirely excluded.

Radiation Dosimetry: As you are well aware, there is some degree of uncertainty regarding the amount of P-32 ingested by the researcher. This reflects the inherent variability of urine bioassay data and, in the case of a pure beta-emitter such as P-32, the difficulty in precisely quantifying retained activity by whole-body counting. Moreover, the interpretation of these data depends on the use of statistical fitting and mathematical modeling techniques that may properly characterize the kinetics of the radionuclide in an "average" subject, but do not necessarily reflect the real kinetics in any individual subject. Some additional uncertainty in this case is introduced by the fact that the chemical identity of the P-32 compound ingested is not known. It is not clear whether the ingested material was in the form of P-32 inorganic phosphate or a P-32 labeled nucleoside or nucleotide. For practical purposes, these organic forms would functionally behave on ingestion like inorganic phosphate (because of degradation of the organic form in the gastrointestinal tract). The possibility that the ingested P-32 was incorporated in an entirely different chemical form, with much different absorption, excretion, metabolism, and biodistribution compared with inorganic phosphate, has not been excluded.

Despite these inherent limitations in the data and in the assumptions used to evaluate the ingested activity and radiation dosimetry, the estimates obtained by the licensee, by RIDIC, and by LLNL are all reasonably close. With the several different calculation methods employed, estimates of the ingested activity range from 300 µCi to 1300 µCi. The best estimate of intake obtained by Michael Stabin at RIDIC is 820 µCi. The best estimates obtained by David Hickman at LLNL, based on several different computational methods, are 1100, 1300, and 1050 µCi, respectively. The average of these four intake estimates is 1068 µCi. The effective dose equivalent to the researcher is estimated (using reference woman rather than reference man assumptions) to be 8.0 rem by RIDIC, and 10.8, 12.7, and 10.3 rem, respectively, for the three different computational methods employed by LLNL. The average effective dose, taken as the average of these four estimates, is 10.4 rem. The corresponding fetal doses are estimated to be 5.1, 6.9, 8.1, and 6.5 rem, respectively. The average fetal dose, taken as the average of these four estimates, is 6.6 rem

As I have indicated in earlier communications with NRC staff, I do not consider myself to be an expert in the interpretation of bioassay data or in the estimation of internal dosimetry. Accordingly, I have not presumed to second-guess the estimates made by Mr. Stabin and Dr. Hickman, who are acknowledged experts in these matters. For the purposes of assessing of potential medical effects of this P-32 ingestion, I have used the average doses and the dose ranges given above.

Potential Deterministic Consequences of P-32 Ingestion: Assuming an effective dose to the contaminated researcher of 10.4 rem (range 8.0 to 12.7 rem), no deterministic effects are expected. With P-32, the red marrow dose is of potential greatest concern for adverse deterministic effects. By extrapolation from the Appendix 4 of the dose estimate report prepared by LLNL, the red marrow dose would approximate 39 rem in a female subject whose effective dose was 10.4 rem (range 30 to 47 rem marrow dose for an effective dose range of 8.0 to 12.7 rem). Discernible hematopoietic system effects can be detected following single exposures to the bone marrow of doses as small as 50 rem, but would be quite unlikely with a

smaller dose. Moreover, the modulating influence of low dose rate must be considered in an instance of internal exposure with a radionuclide having a half-life of 14.3 days. The available hematological data available for the contaminated researcher do not show direct evidence for a deterministic effect on her hematopoietic system.

With an assumed fetal effective dose of 6.6 rem (range 5.1 to 8.1 rem), no deterministic effects are expected with a fetus of approximately 17-weeks age. The deterministic effect of most concern at this stage of fetal development would be impairment of brain development (manifested by retardation or reduced intelligence test scores). The studies evaluating the risk of injury to the developing brain have stratified fetuses into those 8-15 weeks of age (post-conception) and those 16-25 weeks of age (post-conception). The age of the fetus at the time of exposure in this case (17 weeks post menstrual age or 15 weeks post-conception age) is at the border between these two groups. Additionally, the radiation dose from P-32 would be delivered over a protracted period of time, thus clearly extending part of the exposure into the older-age stratum. Moreover, it is unknown whether modulation for a low dose rate must also be considered. Irrespective of these points of uncertainty, radiation-induced severe mental retardation is unlikely in this fetus. Although the available data are generally taken to indicate a linear, non-threshold response, they are also consistent with a threshold in the range of 20-40 rem for the 8-15 week fetus, with no definite increase in mental retardation evident at doses less than 20 rem. In fetuses between 16 and 25 weeks of age, no definite increase in mental retardation is evident at doses below 50 rem. With regard to less severe impairment of brain development, the results of intelligence test scores suggest a significant radiation-related decrease in 8- to 15-week fetuses and a less marked effect at 16-25 weeks. With utilization of a linear model, a 21- to 33-point diminution of IQ score is expected with a 100-rem acute exposure to a 8- to 15-week fetus. Hence, ignoring dose-rate effects, a theoretical reduction in IQ of the exposed fetus in this case of 1.4 to 2.2 points (assuming an average dose of 6.6 rem) might be expected. (The range of theoretical reductions in IQ scores extends from a low value of 1.1 to a high value of 2.7 points, with doses ranging from 5.1 to 8.1 rem.) Needless to say, such an effect would be undetectable and any putative relationship to radiation exposure unprovable.

Potential Stochastic Consequences of P-32 Ingestion: The stochastic effect of concern in the contaminated researcher is radiation-induced cancer. Based on the risk estimates in *Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR V.* (Washington, D.C.: National Academy Press; 1990:175), the lifetime risk for fatal cancer with a 10.4-rem exposure is 1.24% for a woman exposed at age 25 and 0.59% for a woman exposed at age 35. (The ranges of these risk estimates are 0.95 to 1.51% for exposure at age 25 and 0.45 to 0.72% for exposure at age 35, for effective doses of 8.0 to 12.7 rem.) The actual risk in this case can be reduced by a factor of 2.0 to 2.5 because the exposure was delivered at a low dose rate. For comparative purposes, note that the lifetime risk of fatal cancer without radiation exposure is approximately 20%.

Although there is moderate uncertainty in the data used for cancer risk estimation as a result of *in utero* radiation exposure, a reasonable estimate of the risk during the first 10-14 years of life for leukemia and other childhood cancers following *in utero* radiation exposure is approximately 0.05% per rem. Accordingly, in this case, with an average fetal effective dose of 6.6 rem, an excess risk of 0.33% is estimated (range 0.26 to 0.40% for effective doses ranging from 5.1 to 8.1 rem). For comparative purposes, the natural risk of childhood cancers is about 0.1%. Thus, the risk is increased by about 330% (range 260 to 400%). However, stated another way, the probability that the exposed fetus will **NOT** develop a radiation-induced

childhood cancer is 99.67% (range 99.60 to 99.74%). It is unknown whether this risk estimate should be reduced because of the low dose rate associated with this internal exposure from P-32.

Dr. David Dooley, who provided consultant services for the researcher and her attorney stated in his letter of 15 April 1996 that the risk of chilhood cancer in this infant was 30 to 150 times that in an unexposed child. He then "reasons" that the uncertainties in the dose estimates in this child and in the published estimates of the risk of radiation-induced childhood cancer justify inflation of the relative risk to 1,000 times that in an unexposed child (which is the number he stated in a 7 December 1995 letter to the *Washington Post*.). I see no scientific justification for the latter reasoning. Moreover, I believe that his calculation of the relative risk is flawed. Specifically, it appears that he has divided the estimated **total-childhood** risk in this infant by the **annual** risk in an unexposed child.

In summary, serious medical consequences are not probable to either the exposed researcher or to her infant as a result of the ingestion of P-32.

Please let me know if you need additional information.

Sincerely yours,

Barry A Siegel MD

Barry A. Siegel, M.D.
Professor of Radiology and Medicine
Director, Division of Nuclear Medicine

BAS:mtc