HEALTH EFFECTS OF PROJECT SHAD CHEMICAL AGENT:

PHOSPHORUS -32

[Radiotoxic Effects]

Prepared for the National Academies
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Spring 2004
ACKNOWLEDGEMENTS

Submitted to Dr. William Page, Program Officer, Advisory Panel for the Study of Long-term Health Effects of Participation in Project SHAD (Shipboard Hazard and Defense), Institute of Medicine, the National Academies.

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The Principal Investigator wishes to acknowledge and thank Matthew Hogan, Linda Roberts, Lawrence Callahan, Judith Lelchook and Emnet Tilahun for research assistance, editorial content assistance, and project input.

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Contract No. IOM-2794-04-001
Health Effects of Phosphorus -32
This report deals primarily with the biological health challenges engendered by the agent that is the subject of the report. Nevertheless, this report also incorporates, by reference and attachment, a supplement entitled "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

The supplement addresses and describes a growing body of health effects research and interest centered upon the psychogenic sequelae of the stress experienced personally from actual or perceived exposure to chemical and biological weaponry. Because awareness of exposure to agents in Project SHAD logically includes the exposed person also possessing a perception of exposure to biochemical warfare agents, the psychogenic health consequences of perceived exposure may be regarded as additional health effects arising from the exposure to Project SHAD agents. This reasoning may also apply to simulants and tracers. Therefore, a general supplement has been created and submitted under this contract to address possible psychogenic effects of perceived exposure to biological and chemical weaponry.

Because such health effects are part of a recent and growing public concern, it is expected that the supplement may be revised and expanded over the course of this contract to reflect the actively evolving literature and interest in the issue.
SPECIAL NOTE ON CITATIONS AND AUTHORITIES

Citations to particular authorities shall be according to the name of the principal author, or in the case of references to an entire book, to the chief editor. The citation shall be appended outside the sentence or last in a series of sentences that cites the information or quotation from that authority.

The year of publication will be appended when necessary to clarify the particular source cited if there are several under the same principal author’s name. If the same author has two works published in the same year, the name of the publication in which it appears will be added for clarification. If the main source is a book, the name of the chief editor will be appended.

All citations will be referred to authorities listed in the “Bibliography with Abstracts” section at the end of this report. If an author's name is cited in the text unambiguously, there will be no parenthetical listing of the source at the end of the sentence and the source in full will appear in the “Bibliography with Abstracts” section.
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I. EXECUTIVE SUMMARY

Phosphorus-32 $^{32}\text{P}$ was first synthesized in the 1930s. It has a physical half-life of 14.3 days and emits a relatively high energy $\beta$ particle. It was the first synthetic radionuclide to be used for human therapy. The isotope has found wide use as a tracer element in both biological and chemical studies.

$^{32}\text{P}$ is one of only 6 radionuclides classified as a human carcinogen. The classification is primarily due to its ability to cause leukemia in PV patients. Sodium $^{32}\text{P}$ phosphate is currently a treatment of choice for polycythemia vera (PV) and essential thrombocythaemia (ET) in the elderly; it is also used to treat bone pain from metastatic disease. Chromic $^{32}\text{P}$ phosphate and other forms of $^{32}\text{P}$ have been used to treat a number of conditions. Sodium $^{32}\text{P}$ phosphate tends to concentrate in the bone, liver and spleen and has a whole body biological half-life of 39.2 days.

Overdoses of sodium $^{32}\text{P}$ phosphate result in haematological disorders such as aplasia, agranulocytosis and severe thrombocytopenia. $^{32}\text{P}$ has been shown to cause cancer when locally deposited in animals. Sodium $^{32}\text{P}$ phosphate has also been shown to cause low sperm counts, thyroid and blood disorders in animals. There is still controversy on whether a dose-response exists for the induction of leukemia and whether $^{32}\text{P}$ would cause leukemia in the general population.

Leukemia is typically seen 5-15 years after exposure. Single exposures can result in chronic effects. Occasional side effects of intraperitoneal instillation of chromic $^{32}\text{P}$ phosphate have included bone marrow depression, pleuritis, nausea, and abdominal cramping.

Acute high exposure responses are non-stochastic. These acute effects usually appear quickly and can result in burns and radiation sickness. The symptoms of radiation sickness can include nausea, weakness, hair loss, skin burns and diminished organ function. At higher levels and exposure durations, system collapse, intestinal lining destruction, bleeding, and death can occur. Eye lens damage from external exposure also can occur, as indicated by the 15 rem yearly limit on eye radiation exposure.
II. BACKGROUND

$^{32}$P is a synthetic radionuclide whose synthesis was first established in the mid-1930s by Ernest Lawrence, Enrico Fermi, and George de Hevesy. (de Hevesy) The first published report of the synthesis of $^{32}$P was by Chiewitz and de Hevesy, who bombarded carbon disulfide with neutrons. They also reported its use as a tracer element in animal studies. (Chiewitz)

De Hevesy was among the first to realize the power of tracer elements in studying both chemical and physiological reactions and was awarded the Nobel Prize in Chemistry in 1943. The first medical use of $^{32}$P was performed shortly thereafter in late 1936 by John Lawrence, the brother of the physicist Ernest Lawrence. Dr. John Lawrence, after successful studies with mice, treated a woman suffering from leukemia with sodium [$^{32}$P] phosphate prepared using Ernest Lawrence’s cyclotron. (Anonymous)

This was the first use of any synthetic radionuclide for a medicinal purpose. Sodium [$^{32}$P] phosphate is still a treatment of choice for polycythemia vera, a myeloproliferative disorder which results in abnormal proliferation of hematopoietic bone marrow cells and an absolute increase in red cell mass and total blood volume. (Berlin)
III. PHYSICAL DATA

Radionuclides can be classified in three ways: 1) the type (particle) of emission during decay, 2) the energy of that emission, and 3) the rate of the emission. $^{32}\text{P}$ decays to $^{32}\text{S}$ through the emission a $\beta^-$-particle with a maximum energy of 1.7 MeV and average emission energy of 0.695 MeV. The physical half-life for $^{32}\text{P}$ decay is 14.3 days. (Baker)

In living tissue, the $\beta^-$-particle has a maximum range of approximately 8 mm and an average range of 2 mm (Baker). In addition to $\beta^-$-particles, $^{32}\text{P}$ emission can lead to the formation of x-rays through a process called bremsstrahlung (braking radiation), which is caused by the slowing of electrons as they pass through shielding material. The production of x-rays is proportional to the atomic mass of the shielding material.

X-ray production is pronounced when high-density materials such as lead are used for direct shielding. For these reasons $^{32}\text{P}$ is usually shielded by Lucite or another plastics that does contains high mass atoms. Lead or even glass should not be used to shield $^{32}\text{P}$ (Reginatto).

The units of radioactivity are as follows: the activity, or extent of radioactivity are measured in curies (Ci) or becquerels (Bq),

Becquerel =1 disintegration per second (s$^{-1}$)

Curie= 3.7x10$^{10}$ disintegrations per second (10 CFR Part 20.1005)

The radiation absorbed dose is measured in Grays or Rads

A Gray is the SI unit and is equal to 1 Joule/kilogram (100 rad)

A Rad is equal to 100 erg/gram.

The dose equivalents are measured in Sieverts or Rems and are equal to the absorbed dose multiplied by a quality factor. The quality factor is dependent on the type of particle emitted, since alpha particles do more damage to tissue than electrons, x-rays or gamma rays their quality factor is equal to 20. Electrons, x-rays and gamma rays have a quality factor of 1; neutrons have a quality factor of 10.
IV. HEALTH ISSUES IN INDUSTRIAL & ENVIRONMENTAL HYGIENE

$^{32}$P like most radionuclides is primarily regulated by the Nuclear Regulatory Commission (NRC). NRC regulations, along with regulations from the Department of Transportation (DOT) and Health and Human Services (HHS), control the manufacture, storage, use, exposure, distribution, and disposal of radionuclides. Radionuclides are essentially controlled from cradle to grave. All facilities that manufacture or use $^{32}$P must be licensed by the NRC and have a trained Radiation Safety Officer.

The extent of exposure for all employees that work with $^{32}$P must be monitored. Exposure of the extremities of employees working with radioactive isotopes is limited to no more than 50 rems of radioactivity per year. The eyes of employees are limited to not more than 15 rems of radioactivity per year. The total effective dose equivalent must not be greater than 5 rem.

Based on these guidelines, the NRC has established annual limits on intake for a variety of radionuclides. The current annual intake limit is 0.6 mCi for $^{32}$P. (10 CFR Part 20). Limits for pregnant workers are significantly lower with an allowance of 500 mrem over the complete term of pregnancy. Exposure of the general public is further limited with maximal exposure limits at 2% of the occupational limit. (10 CFR Part 20) The average amount of exposure in the United States is about 350 mrem per year with about 80% from natural sources and 20% from man-made sources. (NIH Fact Sheet: see below).

<table>
<thead>
<tr>
<th>Natural Sources (82%)</th>
<th>55%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inside Human Body</td>
<td>11%</td>
</tr>
<tr>
<td>Rocks and Soil</td>
<td>8%</td>
</tr>
<tr>
<td>Cosmic Rays from Space</td>
<td>8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Man-Made Sources (18%)</th>
<th>11%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical X rays</td>
<td>11%</td>
</tr>
<tr>
<td>Nuclear Medicine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4%</td>
</tr>
<tr>
<td>Consumer Products&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3%</td>
</tr>
<tr>
<td>Occupational Uses&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.3%</td>
</tr>
<tr>
<td>Fallout from Nuclear Weapons Tests Less than 0.8%</td>
<td></td>
</tr>
<tr>
<td>Nuclear Power Production</td>
<td>0.1%</td>
</tr>
<tr>
<td>Miscellaneous&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Involves the use of radioactive materials in diagnosing and treating patients with cancer and other diseases.

<sup>b</sup> Building materials, tobacco, mining and agricultural products, water supplies, etc.

<sup>c</sup> Uranium mines, industrial and medical users, etc.

<sup>d</sup> Department of Energy facilities, smelters, transportation, etc.

* Source: National Council on Radiation Protection and Measurements, Report No. 83. (Total adds up to more than 100% due to rounding off of percentages.)
V. MEDICAL USES, PHARMACOKINETICS & PHARMACODYNAMICS

As noted in the previous sections, sodium $^{32}$P phosphate was the first synthetic radionuclide ever used in medical therapy. It is currently a treatment of choice for polycythemia vera (PV) and essential thrombocythaemia (ET) in the elderly and is also used for the treatment of bone pain associated with skeletal metastases. The initial dosage range for polycythemia vera (PV) is 1-5 mCi dependent on the severity, stage and size of the patient. (Baker) Although the risk of leukemia is a concern for younger ET and PV patients, the overall effectiveness of sodium $^{32}$P phosphate make it an acceptable therapy for both PV and ET, particularly in the elderly. (Baker, Brandt, Najean, Randi).

The dosage range to treat metastatic bone pain is 10-21 mCi given over a 3-4 week period. A typical regimen is 3 mCi on the first day followed by 2 mCi given every other day during the first week, two doses of 2 mCi during the second and third weeks and 1 mCi given twice a week until a total of 21 mCi has been administered. Treatment is stopped if a patients white blood cell count is less than 3,000 per mm$^3$ or a platelet count of less than 50,000 (Baker).

Pharmacodynamic studies indicate that during the first 3 days intravenously administered sodium $^{32}$P phosphate is distributed uniformly within the phosphate pool throughout the body. Only 5-10% is excreted in the urine during the first 24 hours and approximately 20% during the first week. After 3 days, sodium $^{32}$P phosphate is deposited primarily in the bone marrow, liver and spleen. (Baker) Whole blood studies using PV patients with indicated two-compartment pharmacokinetics with mean half-lives of 1.7 and 22.5 days. The biological half-life in bone marrow varied from 9-27 days depending on the bone. Whole body retention curves however, showed, a single exponential decay with a mean biological half-life of 39.2 days. (Spiers)

In addition to PV, ET, and bone pain, sodium $^{32}$P phosphate has been used to treat chronic myeloid leukemia (CML), chronic lymphocyte leukemia (CLL), multiple myeloma. Sodium $^{32}$P phosphate displayed activity against both CML and CLL but $^{32}$P therapy but was eventually superceded by treatment with alkylating agents. (Roberts)

Chromic $^{32}$P phosphate, a blue-green suspension having a particle size of 0.5-1.5 µm, is used for the treatment of peritoneal or pleural effusions caused by metastatic disease. The suggested dose is 10-20 mCi for intraperitoneal instillation and 6-12 mCi for intrapleural instillation. Treatment is generally well tolerated and palliative relief is achieved in 50-60% of the cases.

Side effects such as bone marrow depression, pleuritis, nausea, and abdominal cramping are occasionally seen. (Baker). Chromic $^{32}$P phosphate and other colloidal $^{32}$P phosphates have been used to treat solid tumors without success. These studies showed
that the colloidal compound is mobilized from the injection point resulting in eventual systemic distribution particularly to the liver. These studies indicated that systemic distribution reduced the potential antitumor activity of $^{32}\text{P}$ (Boye, Zubillaga).

Radioactive stents containing $^{32}\text{P}$ have been used to reduce the rate of restenosis caused by in-stent neointimal hyperplasia. $^{32}\text{P}$ coated stents did not prevent in-stent neointimal hyperplasia but only delayed restenosis with no significant benefit seen after one year (Kay). Radioactive $^{32}\text{P}$ coils have also been used to prevent recanalization after endovascular treatment of intracranial aneurysms (Raymond).
VI. ANIMAL AND CELLULAR STUDIES

A number of animal studies have been performed to assess the oncogenic potential and toxicity of $^{32}$P. Intraglandular injection of 0.25 mCi of chromic colloidal $^{32}$P phosphate resulted in 64% of the rats developing salivary gland tumors seven months postinjection. Fifty percent of the tumors were sarcomas, 36% were carcinomas, and 14% were carcinosarcomas (Espinal).

Chromic colloidal $^{32}$P phosphate injectioned intra-articularly in the knee joint resulted in cancer developing near the site of injection in 70% of the rats over a nine month period (Ubios). Mice injected intraperitoneally with 1.0 mCi/g showed a reduction in blood cell number and a fall in hemoglobin and fall in hemocrit and hemoglobin levels. (Malhotra) A comparision of bone marrow toxicity in mice by $^{32}$P and $^{33}$P phosphate indicated that $^{32}$P phosphate limited the survival of granulocyte-macrophages colony forming cells to a much greater extent than $^{33}$P phosphate. The damage to marrow cells was attributed to the much greater energy of the emitted $\beta^-$particles in $^{32}$P compared to $^{33}$P. (Goddu)

Studies with male mice indicated that $^{32}$P phosphate concentrates into the DNA of sperm cells and resulted in this resulted in testis weight loss and significant decreases in the number of sperm heads. Significant decreases in the number of sperm were seen at doses as low as 0.2 microCi/g body weight of $^{32}$P (Mian). $^{32}$P has also been reported to alter thyroid morphology in mice. A series of experiments performed with mice injected with 1 $\mu$Ci/g of $^{32}$P at very stages of development indicated that the thyroid of mice more than 14 days old and less than 28 days old underwent significant morphological changes in the thyroid. Surprisingly, there was no effect on 18 day-old fetuses on mice as old as 14 days or older than 28 days. The effects of $^{32}$P on mice appear to be dependent on the stage of development. (Dev)

Cellular studies have indicated that $^{32}$P induced more damage to cells than other radionuclides at equivalent doses. (Cooper) Some studies have indicated that the extensive damage caused by $^{32}$P may be due to its incorporation into nucleic acids and the resulting single strand breaks that occur when a phosphate group transforms into a sulfate upon decay. (Zakharov, Cols) Other studies have indicated that damage is primarily due to radiation effects and not due to incorporation into nucleic acids. (Cooper) Again the type and extent of damage may depend on cell type. Sperm cells, which contain a high proportion of DNA, may be particularly sensitive to the damage caused by incorporation into nucleic acid.
## VII. HUMAN STUDIES, TOXIC & ADVERSE EFFECTS

For the most part the effects of radiation are related to duration of exposure and dose. Health effects from radiation can be broken down into two types stochastic and non-stochastic. Non-stochastic are acute events in which the dose is generally very high and the duration short. These acute effects usually appear quickly and can result in burns and radiation sickness. The symptoms of radiation sickness include nausea, weakness, hair loss, skin burns or diminished organ function. Below is chart from the EPA that relates the effect of acute exposures to general health effects (EPA).

<table>
<thead>
<tr>
<th>Exposure (rem)</th>
<th>Health Effect</th>
<th>Time to Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>radiation burns; more severe as exposure increases.</td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td>changes in blood chemistry</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>nausea</td>
<td>hours</td>
</tr>
<tr>
<td>55</td>
<td>fatigue</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>vomiting</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>hair loss</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>90</td>
<td>diarrhea</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>hemorrhage</td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>death from fatal doses</td>
<td>within 2 months</td>
</tr>
<tr>
<td></td>
<td>destruction of intestinal lining</td>
<td></td>
</tr>
<tr>
<td></td>
<td>internal bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>death</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td></td>
<td>2,000 damage to central nervous system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>loss of consciousness</td>
<td>minutes</td>
</tr>
</tbody>
</table>
Stochastic effects are often associated with long-term chronic exposure or long term effects and often include the development of cancer. The relationship between radiation and cancer has been shown in the study of A-bomb survivors in Hiroshima and Nagasaki. These exposures involved mainly $\gamma$-radiations and the relative risk of all cancers in these survivors appears to be increasing with increasing age. Leukemia showed a curious relationship with the rate increasing linearly or quadratically up to 4 Gy and then decreasing between 4-8 Gy (Bier).

$^{32}$P is one of only six radionuclides rated to be carcinogenic in humans by IARC. The other five radionuclides include radium-224, radium-226, radium-228, thorium-232, plutonium-239, and iodine-131. (IARC). There are three major concerns regarding $^{32}$P phosphate: it is a strong $\beta^{-}$-emitter; it is deposited or concentrated into bone tissue; and because of the nature of the phosphate group it has the potential to be incorporated into nucleic acids and other essential cellular components. As mentioned in the IARC report all $\beta^{-}$-emitters have proven to be carcinogenic in animals. This is true even for $^3$H which emits extremely low energy $\beta^{-}$-particles. (IARC)

The predominant factor cited by IARC for the carcinogenic classification were studies, which showed higher rates of leukemia in patients treated for PV with sodium $[^{32}$P] phosphate. (IARC2). The role of $^{32}$P in inducing acute leukemia in PV patients was first suggested in 1945. (Tinney) This was verified in one of the largest studies of PV treatment, which involved over 1200 patients, and showed that treatment with sodium $[^{32}$P] phosphate resulted in 11% of the patients developing acute leukemia. The rate in the control group, which was not treated with a radionuclide was less than 1%. This study also revealed a dose-response relationship, 24.4% of the patients treated with greater than 30 mCi developed leukemia while only 2.7% of the patients treated with 1-9 mCi did so. In each case, acute leukemia took over two years to develop, new cases were also seen greater than 12 years after exposure. (Modan)

In the wake of these studies, John Lawrence argued that the higher rate of leukemia was due to increased survival and that PV eventually results in leukemia. (Lawrence) A subsequent study compared the rate of leukemia in PV patients treated by phlebotomy, chlorambucil, and $^{32}$P. This study reported a 6% rate of leukemia in patients treated with $^{32}$P over a 6 1/2 year period, an 11% rate in those treated with chlorambucil and a less than 1% rate in those treated with phlebotomy. There was no difference in the survival rate between patient groups (Berk). A more recent study, which involved 682 patients, revealed that 10% of the patients treated with sodium $[^{32}$P] phosphate developed leukemia within 10 years, this increased to 30% after twenty years. This study also showed that there was no increase in carcinoma or myeloid metaplasia in patients treated with $^{32}$P when compared to the general population. The study differed from the results of
Modan et. al, in that no significant dose-response was seen in the incidence of leukemia. (Najean 1996)

A more recent study, by the same French group, involving 483 elderly patients (over 65 years of age at the time of treatment) treated with either sodium $^{32}\text{P}$ phosphate or sodium $^{32}\text{P}$ phosphate and hydrourea (HU) as a maintenance therapy showed a 15% rate of leukemia at 15 years in the group treated with sodium $^{32}\text{P}$ phosphate alone. The group treated with HU and sodium $^{32}\text{P}$ phosphate displayed a 30% rate at 15 years. This study also failed to show a dose-response relationship but does indicate that there may be synergistic or additive effects between $^{32}\text{P}$ and other chemical agents in the induction of leukemia (Najean 1998).

One outstanding question is the carcinogenic potential of $^{32}\text{P}$ on the normal population. All of the data used to classify $^{32}\text{P}$ as carcinogen was based on its effect in patients with PV. PV is a disease involving hemopoietic cells as is leukemia and PV patients may be more susceptible to leukemia.

**Overdoses/Poisonings**

There have been several reported cases of accidental overdoses of sodium $^{32}\text{P}$ phosphate in PV patients. In three cases, involving a tenfold overdose, bone marrow aplasia, agranulocytosis and severe thrombocytopenia were seen. Two of the patients recovered completely within six weeks but in one patient a mild thrombocytopenia persisted. One patient followed for over 15 years and two followed for 5 years did not suffer a relapse of PV nor leukemia. (Gmur, Holy)

In 1996, the NRC reported that there were 10 known incidents of deliberate poisoning in the United States involving $^{32}\text{P}$ in research laboratories over previous 20 years. One of the most publicized cases occurred at NIH in 1995 and involved ingestion of $^{32}\text{P}$ by 26 researchers including a pregnant female researcher who ingested between 820 and 1,300 $\mu$Ci of $^{32}\text{P}$, and had an internal committed effective dose between 8.0-12.7 rem. Fortunately, the scientist gave birth to a healthy child and there were no immediate toxic effects that were apparent from the exposure (Watanabe). Animal studies had previously shown that fetal tissues are somewhat resistant to radiation in that there was no increased frequency of tumors in animals with prenatal exposure to $^{32}\text{P}$. Tumors that did occur, however, showed a tendency to occur earlier in treated animals when compared to untreated controls. (Berry)

Another well-studied case occurred in Taiwan and involved the repeated poisoning of a graduate student with $^{32}\text{P}$ and laboratory chemicals. Over a period of approximately two years beginning in 1994, $^{32}\text{P}$ and laboratory chemicals, such as acrylamide, were added to the student’s drinking glass and eating utensils. Shortly after the poisoning began the student developed frequent diarrhea, poor appetite, loss of body weight and facial hair. Although there were no hematological disorders immediately following exposure, the patient developed leukopenia approximately one year after poisoning ceased. (Chao)
VIII. PSYCHOGENIC EFFECTS

No particular study of psychogenic effects of exposure is known. The psychogenic effects in general of being exposed to a contaminant, particularly in the context of weapons of mass destruction, are treated in the supplement “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents”.
IX. NOTE ON SECONDARY SOURCES

The material in the Department of Defense’s “Disclosure of Information on Project 112” addresses the risk of cancer, although the issue does not appear to be as settled on the dose-time relationship to cancer as the content indicates. [http://deployment link.osd.mil/current_issues/shad/final_report/disclose].

X. BIBLIOGRAPHY WITH ABSTRACTS


Berlin N et al. 2003 Polycythemia vera. Hematol Oncol Clin North Am. 17:1191-210. Abstract: The differential diagnosis of an elevated hematocrit and the criteria for the diagnosis of polycythemia vera present little or no problem; however, there is not a consensus on therapy. Spivak likened this to a conundrum--"an intricate and difficult problem." Nonetheless, it can be argued that on the basis of the following criteria--life expectancy, the absence of toxicity, and long remissions an average of 3.1 years or a median of 2 years--and with acute leukemia no more common than in other regimens except phlebotomy alone (a regimen that cannot be sustained), 32P should be the treatment of choice except in pregnant women. Others, but not all, share this view. This is in contrast to the statement, "Thus chemotherapy treatment of [polycythemia vera] patients is not as easy, innocuous, and well tolerated as it is generally believed". Patients treated with phlebotomy alone were subjected to an unacceptably high incidence of early thrombotic events. Unavailability of pipobroman eliminates this choice.


Boye E, et al., 1984 Whole-body distribution of radioactivity after intraperitoneal administration of 32P colloids. Br J Radiol. 57:395-402. Abstract: The whole-body distribution of radioactivity after intraperitoneal instillation of 32P-labelled chromic hydroxide particles has been studied in patients operated for early-stage ovarian cancer. Gamma-camera imaging of the abdominal 32P-distribution revealed that the administration procedure was critical for obtaining a homogeneous plating of the radiocolloids on the serosal surface. Dose calculations based on a uniform distribution of 32P in a capillary layer covering the intraperitoneal surface gave an estimated tissue surface dose of about 30 Gy per 370 MBq of 32P administered. The amount of 32P in peripheral blood increased for seven days after instillation followed by a continuous decrease. Bone marrow concentration was from two to five times as high as that in blood, but the total amounts were too small to give significant radiation doses. Gel chromatography showed that 33% of the activity in blood consisted of high molecular weight material, probably colloids. The remainder of the activity (67%) was attached to material of very low molecular weight, appearing as a consequence of physiological degradation of the colloids.

Abstract: Dose estimation was conducted for internal phosphorus-32 exposure in one young male subject from repeated oral mis-ingestion for > 1 year. Since disclosure for previous continuous contamination, a series of urine samples were collected from this individual weekly for a period of >2 months. P-32 radioactivity in urine samples were measured by the acid precipitation method. Estimation for retrospective total effective dose equivalent received by this subject was conducted for cumulative internal dose estimation. A minimum of 9.4 mSv was estimated for an assumed single ingestion. As this was a rare case in radiation protection and internal radiation dosimetry, its implications were of considerable significance.


Abstract: Theoretical calculations showed that biosynthetic radiolabeling of cells using typical concentrations of 32P (1 mCi/ml) resulted in high radiation doses (200-500 rad/h) being absorbed by the cells. Subsequent investigations with a mouse myelomonocytic leukemia cell line (WEHI-3B(D+)) showed significant loss of replicative ability during brief (less than 1 h) exposures to 1 mCi/ml of 32P. Complete loss of cell replicative ability was found with isotopic doses less than 100 rad (i.e., 100 muCi/ml for 5 h). Experiments employing a less radiosensitive pre-B-cell line (18.81) revealed that significant loss of viability occurred during incubation with 32P under identical conditions to those employed for the WEHI-3B(D+) cell line. Control experiments utilizing decayed batches of 32P and physical separation of the isotope solution from the cells confirmed that the cytotoxicity was caused by radiation emission rather than the presence of toxic components in the isotopic solution. The radiation doses absorbed by cells biosynthetically labeled with 59Fe, 33P, 35S, and 14C were calculated. Although significant levels of radiation can be absorbed 32P was considerably more radiotoxic than the other isotopes. The results of calculations indicated that the judicious choice of container geometry could reduce the absorbed radiation dose from 32P solutions. In particular the biosynthetic radiolabeling of cells in capillary tubes (diameter less than 1 mm) can reduce the absorbed rate to less than one-tenth of the dose received by cells suspended in Petri dishes or centrifuge tubes.


Abstract: When circular single-stranded DNA of phage S13 is labelled with 32P or 33P, the transmutations very efficiently bring about a loss of phage infectiousness (efficiency = 1 for 32P and 0.73 for 33P). For both radionuclides, the lethal efficiencies as well as the lethal events are different. In the case of 32P, the lethal event is the loss of the circular integrity of the DNA molecule, occurring as a consequence of a systematic single strand-break caused by each 32P decay (100%). Conversely, in the case of 33P, the lethal events are either a single strand-break (40%) or a local stereochemical modification (33%). The same primary event, the substitution at each 33P decay of a phosphate by a sulfate molecule, leads to one of these lethal events in relation to the decay site. Moreover,
neither the phage adsorption nor its genome injection into bacteria depends on the physical state of the genome, and thus lethality is revealed at only the genetic level.

**De Hevesy G, 1944** Some applications of isotopic indicators, Nobel Lecture, December 12, 1944 found at [http://www.nobel.se/chemistry/laureates/1943/hevesy-lecture.pdf](http://www.nobel.se/chemistry/laureates/1943/hevesy-lecture.pdf)


**Abstract:** A study has been made on the effects of P-32 on the developing thyroid gland of Swiss albino mice. The series of experiments reveal that: (I) P-32 at the dose rate of 1.0 muCi/g body-weight to the seven-day pregnant mouse has almost no effect on the 18-day foetus or as late as 14-day postnatal thyroid. (II) With the same dose, when given to one-day-old mouse, signs of dead mitotic figures are noticed. The effects are more pronounced in the beginning, but after the fourth week no morphological changes are seen. (III) When a seven-day-old animal is injected with the same dose, dead cells are found in the earlier stages followed by the damage to the vascular structure of the epithelium. (IV) The 14-day injected group shows damage to the epithelium in the form of condensed nuclei and loss of colloid from the follicles. Replacement of follicles by fatty degeneration is evident. (V) A maximum susceptibility to P-32 irradiation is shown by 21-day-old injected animals, where epithelial desquamation and replacement of follicles by fatty degeneration are easily marked one week after the injection. (VI) In the last group, where P-32 is given at the 28th day after parturition, there may be a tendency of the thickening of the blood vessels. (VII) The females show a greater damage to P-32 injection than the males in the postnatal period studied.

**EPA, Understanding Radiation: Health Effects 2004** found at [http://www.epa.gov/radiation/understand/health_effects.htm](http://www.epa.gov/radiation/understand/health_effects.htm)


**Abstract:** The oncogenic power of 32P was demonstrated in salivary glands. An intraglandular injection of 0.25 mCi of chromic colloidal phosphate (32P) was administered to young adult Wistar rats. Seven months post-injection, tumors began to appear in the neck region in 64% of the rats. The tumors were sarcomas (50%), carcinomas (35.70%), and carcino-sarcomas (14.28%).


**Abstract:** Several bone-seeking radiopharmaceuticals, such as 32P-orthophosphate, 89Sr-chloride, 186Re-1,1 hydroxyethylidene diphosphonate (HEDP), and 153Smethylene diamine tetramethylene phosphonic acid (EDTMP), have been used to treat bone pain. The major limiting factor with this modality is bone marrow toxicity, which arises from the penetrating nature of the high-energy beta particles emitted by the radionuclides. It has been hypothesized that marrow toxicity can be reduced while maintaining therapeutic efficacy by using radionuclides that emit short-range beta particles or conversion electrons. In view of the significant clinical experience with 32P-
orthophosphate, and the similarity in pain relief afforded by 32P-orthophosphate and
89Sr-chloride, this hypothesis is examined in this study using 32P- and 33P-
orthophosphate in a mouse femur model. METHODS: Survival of granulocyte
macrophage colony-forming cells (GM-CFCs) in femoral marrow was used as a biologic
dosimeter for bone marrow. 32P- and 33P-orthophosphate were administered
intravenously, and GM-CFC survival was determined as a function of time after injection
and, at the nadir, as a function of injected activity. The kinetics of radioactivity in the
marrow, muscle, and femoral bone were also determined. The biologic dosimeter was
calibrated by assessing GM-CFC survival at its nadir after chronic irradiation of Swiss
Webster mice with exponentially decreasing dose rates of gamma rays (relative biologic
effectiveness equivalent to that of beta particles) from a low-dose rate 137Cs irradiator.
Dose-rate decrease half-times (T_d) (time required for 137Cs gamma ray dose rate to
decrease by one half) of 62, 255, and 425 h and infinity were used to simulate the dose
rate patterns delivered by the radiopharmaceuticals as dictated by their effective
clearance half-times from the mouse femurs. These data were used to experimentally
determine the mean absorbed dose to the femoral marrow per unit injected activity.
Finally, a theoretical dosimetry model of the mouse femur was developed, and the
absorbed doses to the femoral marrow, bone, and endosteum were calculated using the
EGS4 Monte Carlo code. RESULTS: When the animals were irradiated with
exponentially decreasing dose rates of 137Cs gamma rays, initial dose rates required to
achieve 37% survival were 1.9, 0.98, 0.88, and 0.79 cGy/h for dose rate decrease half-
times of 62, 255, and 425 h and infinity, respectively. The D37 values were 144 +/- 15,
132 +/- 12, 129 +/- 3, and 133 +/- 10 cGy, respectively, compared with a value of 103
cGy for acute irradiation. When 32P and 33P were administered, the injected activities
required to achieve 37% survival were 313 and 2,820 kBq, respectively. Theoretical
dosimetry calculations show that 33P offers a 3- to 6-fold therapeutic advantage over
32P, depending on the source and target regions assumed. CONCLUSION: The low-
energy beta-particle emitter 33P appears to offer a substantial dosimetric advantage over
energetic beta-particle emitters (e.g., 32p, 89Sr, 186Re) for irradiating bone and
minimizing marrow toxicity. This suggests that low-energy beta or conversion electron
emitters may offer a substantial advantage for alleviation of bone pain as well as for
specifically irradiating metastatic disease in bone.

Gmur J, et al., 1983 Spontaneous hematologic recovery from bone marrow aplasia after
Abstract: Two patients with polycythemia vera received intravenously an accidental
tenfold overdosage of radiophosphorus therapy (60 and 50 mCi 32P, respectively). In
both patients, the occurrence of hemorrhagic complications 3 wk after the 32P
medication led to detection of the error and referral to our hospital. Upon admission they
showed an agranulocytosis, severe thrombocytopenia, and bone marrow aplasia. In both
cases, spontaneous recovery of the hematopoiesis was observed from day 40
posttreatment onward. In one patient, a slow but ultimately complete normalization of
blood counts and marrow morphology took place, whereas in the other, a mild
thrombocytopenia persists. Nearly 5 yr after the accidental overdosage, both patients are
clinically well. Symptoms of polycythemia vera have not reappeared up to now. Attempts
were made to evaluate the radiation dose absorbed by the bone marrow. In the first
patient, the daily 32P excretion was determined from day 22 to day 60, whereas in the other patient a whole body count was performed on day 78 after administration. From these results, an approximate cumulative bone marrow dose of 10 Sv (1000 rem) could be calculated.


**Abstract:** The follow-up of a 93-year-old-patient with polycythemia vera (PV) diagnosed in 1977 is presented. The patient accidentally received a ten-fold overdose of radioactive P32 due to an incorrectly labelled vial. 14 days after the administration of the overdose of P32, the patient was admitted to the University Hospital of Zurich with bone marrow aplasia. She recovered from the aplasia within 6 weeks. During the following 15 years she has suffered no relapse nor developed leukemia as a secondary complication.


**Summary:** A working group of 23 experts from 8 countries met in Lyon to evaluate the evidence for carcinogenicity of ionizing radiation from internally deposited radionuclides. Another 3 experts participated in the drafting of working papers but were unable to attend the meeting. This was the second of two meetings on ionizing radiation, as recommended by an Ad-hoc *IARC Monographs* Advisory Group on Physical Agents (April 1998; IARC Internal Report No. 98/002, available on this website). Evaluations of carcinogenicity are summarized in the Table.

For purposes of this Monograph, ‘internally deposited’ refers to radionuclides in dispersed forms (e.g., dusts, suspensions, solutions, or gases) that enter the body through inhalation, ingestion, by some form of injection, or, in some cases, by percutaneous absorption. Radionuclides may also enter tissues within removable objects, such as radioactive beads, needles, etc. which may be implanted surgically for therapeutic purposes, or other kinds of fragments implanted accidentally. These kinds of exposures are not considered in this volume. Also not considered are radionuclides (e.g., iron-55, gallium-67) which undergo radioactive decay through processes that do not include emission of either α or β particles.

Radon and its decay products were previously evaluated in *IARC Monographs* Volume 43 (1988) as carcinogenic to humans (Group 1). The subsequently published scientific literature on occupational and residential exposures to radon was reviewed and included in this volume as an update, but no re-evaluation of radon was considered necessary. Six specific radionuclides of the elements radium, thorium, plutonium and phosphorus, plus mixed radionuclides of iodine, were evaluated as carcinogenic to humans (Group 1) on the basis of sufficient evidence for increased risk of cancer in exposed individuals. These include radium-224, radium-226, radium-228, thorium-232 (administered in colloidal form as thorium-232 dioxide), plutonium-239 (exposure to which also entails exposure to plutonium-240 and other isotopes of plutonium), radioisotopes of iodine including iodine-131, and phosphorus-32. Evidence for increased cancer risk in exposed humans is from medical usage in the cases of radium-224, thorium-232 and phosphorus-
32, and from occupational or accidental/environmental exposures for plutonium-239, radium-226 and radium-228, and the radioiodines. In addition, the following global evaluations of two broad categories of internally deposited radionuclides were made on the basis of carcinogenicity in experimental animals plus other relevant data:

Internally deposited radionuclides that emit α particles are carcinogenic to humans (Group 1).

In making this overall evaluation, the Working Group took into consideration the following:

- α Particles emitted by radionuclides, irrespective of their source, produce the same pattern of secondary ionizations and the same pattern of localized damage to biological molecules, including DNA. These effects, observed in in-vitro systems, include DNA double-strand breaks, chromosomal aberrations, gene mutations, and cell transformation.
- All radionuclides that emit α particles and that have been adequately studied, including radon-222 and its decay products, have been shown to cause cancer in humans and in experimental animals.
- α Particles emitted by radionuclides, irrespective of their source, have been shown to cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans in vivo.
- The evidence from studies in humans and experimental animals suggests that similar doses to the same tissues—for example lung cells or bone surfaces—from α particles emitted during the decay of different radionuclides produce the same types of both non-neoplastic effects and cancers.

Internally deposited radionuclides that emit β particles are carcinogenic to humans (Group 1)

In making this overall evaluation, the working group took into consideration the following:

- β Particles emitted by radionuclides, irrespective of their source, produce the same pattern of secondary ionizations and the same pattern of localized damage to biological molecules, including DNA. These effects, observed in in-vitro systems, include DNA double-strand breaks, chromosomal aberrations, gene mutations and cell transformation.
- All radionuclides that emit β particles and that have been adequately studied, have been shown to cause cancer in humans and in experimental animals. This includes hydrogen-3 (tritium), which produces β particles of very low energy, but for which there is nonetheless sufficient evidence of carcinogenicity to experimental animals.
- β Particles emitted by radionuclides, irrespective of their source, have been shown to cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans in vivo.
- The evidence from studies in humans and experimental animals suggests that similar doses to the same tissues—for example lung cells or bone surfaces—from β particles emitted during the decay of different radionuclides produce the same type of non-neoplastic effects and cancers.
**Summary:** Phosphorus

The risk for acute leukaemia is clearly increased in patients with polycythaemia vera who were treated with phosphorus-32 in comparison with those given treatments that did not involve irradiation. However, as polycythaemia vera is a clonal malignancy of the pluripotent haematological stem cells, patients with this disease may be more sensitive to the leukaemogenic effects of irradiation than the general population.


**Abstract:** BACKGROUND: Restenosis after conventional stenting is almost exclusively caused by neointimal hyperplasia. Beta-particle-emitting radioactive stents decrease in-stent neointimal hyperplasia at 6-month follow-up. The purpose of this study was to evaluate the 1-year outcome of (32)P radioactive stents with an initial activity of 6 to 12 microCi using serial quantitative coronary angiography and volumetric ECG-gated 3D intravascular ultrasound (IVUS). METHODS AND RESULTS: Of 40 patients undergoing initial stent implantation, 26 were event-free after the 6-month follow-up period and 22 underwent repeat catheterization and IVUS at 1 year; they comprised half of the study population. Significant luminal deterioration was observed within the stents between 6 months and 1 year, as evidenced by a decrease in the angiographic minimum lumen diameter (-0.43+/-.56 mm; P:=0.028) and in the mean lumen diameter in the stent (-0.55+/-.63 mm; P:=0.001); a significant increase in in-stent neointimal hyperplasia by IVUS (18.16+/-.59 mm(3) at 6 months to 27.75+/-.59 mm(3) at 1 year; P:=0.001) was also observed. Target vessel revascularization was performed in 5 patients (23%). No patient experienced late occlusion, myocardial infarction, or death. By 1 year, 21 of the initial 40 patients (65%) remained event-free. CONCLUSIONS: Neointimal proliferation is delayed rather than prevented by radioactive stent implantation. Clinical outcome 1 year after the implantation of stents with an initial activity of 6 to 12 microCi is not favorable when compared with conventional stenting.


**Abstract:** Swiss albino mice at different stages of their postnatal development (one day, one week, two weeks, three weeks, four weeks age groups) were injected intraperitoneally with radioactive phosphorus (P-32) at the dose of 1.0 muCi/g body weight and studied for their hematological response at weekly intervals up to six weeks of age when they attain sexual maturity. In all the treated groups in both males and females, the radiation injury was evident after injection of radioactive phosphorus. Animals showed reduction in blood cell number and fall in hemoglobin and hematocrit levels after injection. Reparation was also evident in the animals after some lapse of time.
following P-32 administration. Morphological changes in different white blood cells were not observed. No radiation sickness symptoms were observed in any of the treated groups during the study. There was no radiation mortality. The radiation damage to blood forming organs was moderate. It was observed that the females showed a greater hematological damage than the males.


Abstract: Radiation dose to mouse testis was estimated to be about 1.65 rad per microCi of intravenously injected 32P. This high dose to the organ was due to the incorporation of this isotope into the macromolecules of the testis. Up to 30% of the total testis activity was in DNA molecules. Biologic effects on mouse testis from 32P were determined by testis weight loss and the decrease in the number of sperm heads in the testis. Number of sperm heads reached a minimum of 1.3% of control 36 days after injection of 3.5 microCi/g body weight of 32P. Significant decreases in sperm head counts were observed after as little as 0.2 microCi/g body weight of 32P.


Abstract: An analysis of the risk of progression towards leukemia, carcinoma and myelofibrosis was performed in 93 patients treated by 32P alone (PVSG protocols) since 1970-1979, 395 patients over the age of 65 years treated by 32P with or without maintenance therapy using hydroxyurea (French protocol) since 1980-1994, and 202 patients under the age of 65 treated by either hydroxyurea or pipobroman since 1980. The risk of leukemia, or myelodysplasia, or lymphoma in the 32P-treated patients was 10% at the 10th year, but increase after that time to reach a value of about 30% at the 20th year, in the surviving case. This risk was not dose-related. Despite a marked reduction of the cumulative 32P dose in the patients maintained by hydroxyurea, the actuarial risk was 19% at the 10th year. In the patients treated exclusively by non radio-mimetic agents (hydroxyurea or pipobroman) a risk of 10% at the 10th year was observed. The risk of carcinoma (excluding skin cancers) was about 15% at the 10th year in the 32P-treated cases, a value similar to that generally reported by the French statistics. There was no prevalence of digestive carcinomas. In contrast, the patients receiving 32P and hydroxyurea as maintenance had an excess risk: 29% at the 10th year. In the relatively young cases treated by non radio-mimetic agents, the risk was similar in both arms: 9% at the 10th year, similar to the expected incidence at this age. The risk of myelofibrosis with myeloid metaplasia was still relatively low at the 10th year, about 15% in all arms, but increased towards a value higher than 30% in the patients surviving at the 20th year. At the present time, but in only a few cases with long-term following, no myelo-fibrosis with splenic metaplasia has been observed in the pipobroman-treated cases. The present results, which need to be confirmed (the present analysis has been done in spring 95)
suggest that: the use of non radio-mimetic agents does not protect against leukemic transformation, which may be a consequence of the disease; rather than of the treatment,-maintenance therapy after initial use of 32P increases the risk of both leukemia and carcinoma,-and hydroxyurea does not delay the risk of developing myelo-fibrosis, in comparison with 32P alone.


Abstract: AIMS: To compare by a prospective study in high risk polycythemia vera (PV) patients 33P alone and 32P followed by low-dose hydroxyurea (HU) maintenance therapy. Toxicity, efficiency, and leukemogenic potential were studied. PATIENTS: 483 patients with a documented PV, aged more than 65 years at diagnosis, were included between 1980 and 1996 in a prospective study comparing 32P alone and 32P followed by low-dose HU maintenance therapy. Blood cell counts were performed every two months and a clinical evaluation by a specialist was obtained every four or six months. RESULTS: Treatments were well tolerated, but chronic leg ulcers were observed in the maintenance therapy arm. The risk of leukemia was about 15% at the 15th year in the group of patients treated by 32P alone, but reached 30% in the group receiving maintenance therapy. In both arms, there was no significant correlation between occurrence of leukemia and the total dose of 32P. There was a correlation between the leukemic risk and disease severity, estimated on the frequency of relapse. Cancer occurrence was slightly higher than expected in the maintenance arm. HU treatment did not protect against progression to myelofibrosis, probably due to the lack of maintenance of an efficient myeloid or megakaryocytic suppression. Median life-span was slightly shorter in the group receiving HU maintenance. In all cases, life-span was only one year lower than that observed in the reference population. CONCLUSION: For all these reasons, we suggest the use of 32P alone in elderly patients; complementary chemotherapy should only be prescribed in the cases with short-term relapse, and late resistance to 32P.

NIH Fact Sheet: 2004 What We Know About Radiation found at http://www.nih.gov/health/chip/od/radiation/ - xtwo


Abstract: BACKGROUND AND PURPOSE: Endovascular treatment of intracranial aneurysms is safe and effective but is associated with angiographic recurrences. Beta radiation prevents recanalization after coil embolization in experimental models. We wanted to assess the feasibility of using radioactive coil embolization to improve long-term results of endovascular treatment. METHODS: Platinum coils were ion-implanted with 0.13 to 0.26 microCi/cm of 32P. Forty-one patients aged 34 to 84 years with 44 aneurysms with a high propensity for recurrences were included. Radioactive coils were introduced into aneurysms to reach a target volumetric activity of 0.018 microCi/mm3. Nonradioactive coils were also used to ensure the same safety and the same angiographic results as the standard procedure. Angiographic results, procedure-related complications, and neurological events during follow-up were recorded. Angiographic follow-up data
are available in 36 lesions 6 months after treatment. RESULTS: Forty of 44 aneurysms (91%) could be treated with radioactive coils. Target activities could be reached in 88% of lesions that could actually be coiled (35/40). Total activities ranged from 1.72 to 80.9 microCi, for a mean of 20.13+/−20.80 microCi. Procedure-related complications occurred in 7% of patients. Initial angiographic results were satisfactory (complete occlusions or residual necks) in 75% of lesions. Angiographic recurrences occurred in 11 (31%) of patients followed, within the expected range for standard coils. There was no complication from beta radiation during a mean follow-up period of 10 months. CONCLUSIONS: Radioactive coil embolization is feasible; target volumetric activities can be reached in most aneurysms considered for endovascular treatment.


Abstract: Following the development of the cyclotron in 1932, radio-isotopes became available for use in medicine both as tracer substances and therapeutic agents. The father of nuclear medicine, Dr J. H. Lawrence, pioneered their use in a range of disease states and found that radio-isotopes were of enormous value in the diagnosis and treatment of haemopoietic disease, particularly the myeloproliferative disorders. Radioactive phosphorus 32P emerged as the radio-isotope of choice for the myelosuppressive treatment of myeloproliferative disorders. This article also describes the use of radio-isotopes in the treatment of other disorders: chronic myeloid leukaemia, chronic lymphocytic leukaemia and myeloma, work that is now largely forgotten. All myeloproliferative disorders may evolve without treatment into myelodysplastic syndrome or blast-cell transformation. It is accepted that life is prolonged in myeloproliferative disorders treated with 32P or alkylating agents, yet both are leukaemogenic. The ideal form of treatment for polycythaemia vera is unknown and will remain so, for patients with this disorder often outlive their physician and achieve 90% of normal life expectation. 32P remains the treatment of choice for elderly patients with polycythaemia vera.


Abstract: This paper reports the determination of absorbed dose to bone marrow in the treatment of polycythaemia by 32P, based on the measurement of activities in bone and marrow biopsies taken at various times from 1 to 27 days after injection of the radionuclide. Activities were measured in the cortex, trabeculation and marrow of biopsies taken from the iliac crest, and also in sternal marrow. The biological half-life of 32P in marrow from the iliac crest was found to be nine days; that derived for sternal marrow was lower, but the difference was not statistically significant; the value for trabecular bone was 27 days. The biological half-life for 32P in the body, as measured by whole-body counting, was 39 days. Calculations of the dose-rate to trabecular marrow have been made by a method based on that of Whitwell and Spiers (1971), but modified to allow for the presence of 32P in the marrow as well as in trabecular bone. The dose-
rates follow a single exponential decay with a half-life of 6.7 days. The integrated dose including that during the first day is 24 rad per mCi injected.


**Abstract:** Chronic colloidal phosphate labeled with 32P, which has been proposed for the treatment of several articular diseases, was injected intra-articularly in the knee joint of adult Wistar rats. After a 270 days minimum latent period, tumors began to appear in the injected zone, to a 70% frequency. Ten lung metastases were detected. In five cases, squamous cell carcinomas were induced in the injected area. The relevance of a sound evaluation of the risk involved in treatments with radioactive isotopes, is discussed.


**Zakharov IA, et al., 1978** Mutagenic effect of the decay of 32p incorporated into mRNA. *Genetika.* 14:1838-41

**Abstract:** The transcription of Escherichia coli lactose operon was induced and the conditions for 32P maximal incorporation into mRNA which is synthesized on this operon were made. The complex between mRNA and DNA has been fixed. The DNA complementary strand has been damaged with the 32P desintegration. The induction of mutants incapable of lactose utilization has been observed. It is shown that the number of such mutants in the experiments with 32P and with the inducer is twice as much as in the cheek experiments with 32P only.


**Abstract:** In order to evaluate the effectiveness of an intratumorally single dose of chromic [32P] phosphate for the treatment of solid tumors, studies of bioelimination, biodistribution, and therapeutic action were carried out. Only for comparative purposes were similar studies undertaken using a solution of sodium [32P] orthophosphate-gelatin. Results show that when sodium [32P] orthophosphate-gelatin was intratumorally injected, the percentage of total elimination, after 32 days of treatment, was equal to 85.90 +/- 8.70%, with a higher percentage in urine (64.50 +/- 13.70%) than in feces (21.40 +/- 4.50%). In biodistribution studies, the greater percentage was found in bone (15.54 +/- 2.21%), whereas only 2.51 +/- 0.39% remained in the tumor. When chromic [32P] phosphate was intratumorally injected, we found that the total elimination was equal to 51.70 +/- 6.90%, with a higher amount in feces (32.70 +/- 4.80%) than in urine (19.00 +/- 3.60%). Biodistribution studies demonstrated that 28.93 +/- 1.30% was still in the tumor and 19.01 +/- 1.30% of the injected activity was found in the liver. On the other hand, when therapeutic action was evaluated, no tumoral regression was observed. These results demonstrate that the colloid of chromic [32P] phosphate cannot be used in the
treatment of solid tumors as it mobilizes from the injection point, delivering a high dose to the entire organism.