



10th International Conference on the Health Effects of Incorporated Radionuclides
10-14 May, 2009
La Fonda Hotel, Santa Fe, New Mexico, USA

Conference Program

Sunday, 10 May 2009

4pm – On Site Registration, La Terraza Room
6pm - Welcome Reception, La Terraza Room

Monday, 11 May 2009

7am – On Site Registration and Continental Breakfast, Ballroom

AM Session

8:30 am - Introduction and Opening Remarks
R. Guilmette

EPIDEMIOLOGY ON INTERNALLY DEPOSITED RADIONUCLIDES

D. Melo, Chair

8:50 am - Life Span Study on Late Effects of Radium-224 in Children and Adults
H. Spiess, Invited Speaker (To Be Presented by L. Walsh)

9:10 am - Non-skeletal Malignant Diseases in Patients Treated with Radium-224
E.A. Nekolla, L. Walsh, H. Spiess

9:30 am - Radon and the Risk of Cancer Mortality – Results from the German Uranium Miners Cohort
L. Walsh, M. Schnelzer, A. Tschense, B. Grosche, M. Kreuzer

9:50 am - Leukemia Risk among Czech Uranium Miners in Dependence on Doses from Radon, External Gamma, and Long Lived Radionuclides
L. Tomasek, I. Malatova, J. Marsh

10:10 am – Break

10:40 am - Preliminary Lung Cancer Risk Assessment of Exposure to Radon Progeny for Transylvania, Romania
L.A. Truta-Popa, A. Dinu, T. Dicu, K. Szacsvai, C. Cosma, W. Hofmann

11:00 am - Site-Specific Cancer Risk and Occupational Exposure to Uranium
I. Guseva Canu, S. Jacob, E. Cardis, P. Wild, S. Caër-Lorho, B. Auriol, A. Acker, D. Laurier, M. Tirmarche

11:20 am - Occupational and Medical Exposure to Ionizing Radiation and Leukemia Risk Among German Uranium Miners
M. Möhner, M. Lindtner, J. Gellissen

11:40 pm - Early Effects in Hemopoiesis in Chronic Radiation Exposure of People

A.V. Akleyev, I.V. Akushevich, G.P. Dimov, G.A. Veremeyeva, T.A. Varfolomeyeva, S.V. Ukraintseva, A.I. Yashin

12:00 pm – Lunch, La Terraza Room

PM Session

BIOLOGICAL EFFECTS OF INTERNALLY DEPOSITED RADIONUCLIDES

B. Boecker, Chair

1:00 pm - Toxicity of Alpha-Emitting Radionuclides: from Curie to Litvinenko

J. Harrison, J. Marsh

1:20 pm - Long-term Cellular Effects in Humans Chronically Exposed to Ionizing Radiation

G. Veremeyeva, I. Akushevich, T. Pochukhailova, E. Blinova, T. Varfolomeyeva, O. Ploshchanskaya, O. Khudyakova, A. Vozilova, O. Kozionova, A. Akleyev

1:40 pm - Long Incubation Period from the Induction of Cancer by Thorotrast is Attributed to the Uneven Irradiation of Hepatocytes at the Microscopic Level

Y. Yamamoto, N. Usuda, T. Takatsuji, Y. Kuwahara, M. Fukumoto

2:00 pm - Late-Occurring Pulmonary Pathologies Following Inhalation of Mixed Oxide (U,PuO₂) Aerosol in the Rat

N.M. Griffiths, A. Van der Meeren, P. Fritsch, M.C. Abram, J.F. Bernaudin, J.L. Poncy.

2:20 pm - Carcinogenesis from Inhaled ²³⁹PuO₂ in Beagles: Evidence for Radiation Homeostasis at Low Doses?

D.R. Fisher, R.E. Weller

2:40 pm - The RBE for Lung Cancer in Rats

F.F. Hahn, D.L. Lundgren

3:00 pm - Break

3:30 pm - Measurements of the Relative Toxicity of ²⁴²Cm alpha- and ⁴⁵Ca beta-radiations in Mice.

N.D. Priest, D.Hoel

3:50 pm - Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission of Genetic Damage and Transgenerational Offspring Effects

A.C. Miller, B. LeBlanc, R. Rivas, R. Merlot, L. Crepin, P. Lison

4 :10 pm – Discussion of Posters

F.F. Hahn, Rapporteur

Tuesday, 12 May 2009

7am – Breakfast, Ballroom

AM Session

DECORPORATION OF INTERNALLY DEPOSITED RADIONUCLIDES

N. Priest, Chair

8:00 am - Cuprimine[®] and Syprine[®], FDA-approved Therapeutics for Wilson Disease, are Promising Candidates to Decorporate the High-Energy Radioisotopes Cobalt-60 and Polonium-210

B.L. Levinson, K.D. Thrall, T.G. Levitskaia

8:20 am - Alginate Reduces the Absorption and Retention of Ingested Strontium in the Rat

T.G. Levitskaia, K.D. Thrall

8:40 am - Will Alteration of Radiostrontium Biodistribution by Chlorthalidone Improve Therapy of Painful Bone Metastases?

J.J. Coupal

9:00 am - ¹³⁷Cs Dose Reduction Due to Prussian Blue

D. Melo, J. Lipsztein, L. Bertelli, R. Guilmette

9:20 am - *In Vitro* and *In Vivo* Evaluation of a Novel Decorporation Agent (SAMMS[™]) for Cesium (Cs) in Rats

C. Timchalk, J.A. Creim, R.S. Addleman, G.E. Fryxell, W. Yantasee

9:40 am - Review of Recent Developments and Results in the Field of Radionuclide Decorporation

E. Ansoborlo, F. Taran, R. Burgada

10:00 am – Break

11:00 am - Biomimetic Actinide Chelators: Preclinical Development of Orally Active Decorporation Agents

R.J. Abergel, P.W. Durbin, B. Kullgren, S.N. Ebbe, J. Xu, P.Y. Chang, D. Bunin, E.A. Blakely, K.A. Bjornstad, C.J. Rosen, D.K. Shuh and K.N. Raymond

11:20 am - Pharmacological Properties of Orally Available, Amphipathic Polyaminocarboxylic Acid Chelators for Actinide Decorporation

S.C. Miller, X. Wang, M. B. Bowman.

12:00 pm – Lunch, La Terraza Room

PM Session

1:00pm - Functional Sorbents for Selective Decorporation of Plutonium, Uranium, Thorium, and Americium

W. Yantasee, J.A. Creim, R.S. Addleman, G.E. Fryxell, C. Timchalk

1:20 pm - NIAID/NIH Radiation/Nuclear Medical Countermeasures Development Program

N. Hafer, B. Maidment, D. Cassatt, A. DiCarlo, M. Norman, N. Ramakrishnan, R. Hatchett

1:40 pm - Oral Ca- and Zn-DTPA: Efficacy of Oral Formulations to Decorporate Am-241 from Rats after Acute Exposure

G.N. Shankar, M. Malfatti, M. Sutton, N.K. Bejugam, K. Turtletaub.

2:00 pm - Multidentate Hydroxypyridinonate Chelators for the Actinides: Delayed Oral Treatment

P.W. Durbin, B. Kullgren, S.N. Ebbe, K.N. Raymond

2:20 pm – Break

MONITORING AND ANALYTICAL METHODS

L. Bertelli, Chair

2:50 pm - The Use of Calix[6]arene Molecules for Actinides Analysis in Urine:

An Alternative to Current Procedures

G. Phan, A. Manoury, A. Legrand, F. Rebière, C. Bouvier-Capely

3:10 pm - Uranium Speciation in Drinking Waters from Drilled Wells in Southern Finland and Its Links to Health Effects

O. Prat, H. Vercouter, E. Ansoborlo, P. Fichet, P. Perret, P. Kurttio, L. Salonen

Wednesday, 13 May 2009

7am – Breakfast, Ballroom

AM Session

RADIONUCLIDE BIOKINETICS

F. Paquet, Chair

8:00 am - Determination Of Milk Transfer Coefficients For Four Elements In Four Species Of Grazing Animals

S.L. Simon, A. Bouville

8:20 am - Iodine-131 Biokinetic Study in Ablation Treatment for Thyroid Cancer

A.C.H. Nascimento, J.J.L. Lipsztein, R. Corbo, A.M.O. Rebelo

8:40 am - ¹³¹I-Iodide Organ Doses for Hyperthyroid Patients

D.R. Melo, P. Zanzonico, A. Brill, M. Stabin, P. Vicini, D. Kwon, B. Moroz, A. Bouville, S.L. Simon

9:00 am - Natural Accumulation Of Radium-226 In The Human Thyroid Gland And Health Implications

S.L. Simon, S.A. Ibrahim, A.O. Barden, L. VanMiddlesworth

9:20 am - Quantitative Plutonium Microdistribution In Bone Tissue Of Vertebra From Mayak Worker

Y.V. Lyovkina, S.C. Miller, S.A. Romanov, M.P. Krahenbuhl, M.V. Belosokhov

9:40 am - Break

10:10 am - Development Of A Physiological Bone Model For Modeling Of Radionuclide And Stable Compounds In Humans

R.B. Richardson

10:30 am - Twenty Years of Follow-up for a Hanford Plutonium Wound Case

E.H. Carbaugh, T.P. Lynch, C.L. Antonio, F. Medina-Del Valle

10:50 am - Twelve Years of Follow Up of Cases With Old ²⁴¹Am Internal Contamination

I. Malátová, T. Vrba, V. Bečková, H. Pospíšilová

PM Social Event

11:45 pm – Box Lunch and Tour of Taos Pueblo

Thursday, 14 May 2009

7am – Breakfast, Ballroom

AM Session

DOSE ASSESSMENT

D. R. Fisher, Chair

8:00 am - Dose Coefficients of ^{141}Ce , ^{144}Ce , ^{95}Zr and ^{90}Sr Using Voxel Phantom SAFs for Photons and Electrons

W.B. Li, M. Zankl, H. Schlattl, N. Petoussi-Henß, K.F. Eckerman, W.E. Bolch, U. Oeh, C. Hoeschen

8:20 am - Dose Conversion Factors for Radon – How Should They be Calculated?

J. Marsh, J. Harrison, M. Tirmarche, D. Laurier

8:40 am - Consideration Of Uncertainties In The Monitoring Of Internal Contamination

E. Davesne , P. Casanova , E. Chojnacki , F. Paquet , E. Blanchardon

9:00 am - Modelling Intersubject Variability of Bronchial Doses for Inhaled Radon Progeny

W. Hofmann, R. Winkler-Heil, M. Hussain

9:20 am - Uncertainties in Internal Dose Assessment

A. Bouville, R. T. Bell III, A. L. Apostoaei, A. Birchall, W. Bolch, A. James, K. Kearfott, R.W. Leggett, D. Melo, G. Miller, D. Pawel, C. Potter, G. Sgouros, M. Stabin, R. Toohey

9:40 am - Break

10:10 am - Three Plutonium Chelation Cases at Los Alamos National Laboratory

L. Bertelli, T. L. Waters, G. Miller, M.S. Gadd, M. C. Eaton

10:30 am - Case Study: Three Acute ^{241}Am Inhalations with DTPA Therapy

E.H. Carbaugh, T.P. Lynch, C.N. Cannon, L.L. Lewis

10:50 am - Biokinetic Modeling of DTPA Decorporation Therapy: The CONRAD Approach

B. Breustedt, E. Blanchardon

11:10 am – Wrap-up of Conference

PM Conference Adjourns

POSTERS

Modeling Deterministic Effects in Hematopoietic System Caused by Chronic Exposure to Ionizing Radiation in Large Human Cohorts

I. Akushevich, G. Veremeyeva, G. Dimov, S. Ukraintseva, K. Arbeev, A. Akleyev, A. Yashin

Whole-Body Measurements Of Workers Occupationally Exposed To Radionuclides At Ipen, - Brazil

J. C. S. Cardoso, E. A. R. Berti, M. Xavier

Testing of Individual Sensitivity to Radon and Thoron Exposure by *In Vitro* Irradiation of Lymphocytes Culture

D. Ciorba, F. Eva, C. Cosma, D. Pirv, D. Marcu

Optimization of ^{99m}Tc Measurement in ^{99m}Tc Eluate Samples Using a Scintillation Detection System

A.L.A. Dantas, B.S. Ribeiro, R.S.S. Souza, E.A. Lucena, B.M. Dantas

Evaluation of the Internal Exposure in a ^{123}I Production Plant Through In Vivo Monitoring

B.M. Dantas, J. Regis, F. Araújo, A.L.A. Dantas, E.A. Lucena, M.V.S. Vidal, L. Bertelli

A Mobile Bioassay Laboratory for the Assessment of Internal Doses. Based on In Vivo and In Vitro Measurements

B.M. Dantas, E.A. Lucena, A.L.A. Dantas, M.S. Santos, L.Q.C. Julião, D.R. Melo, W.O. Sousa, P.C. Fernandes, S. Mesquita

Biological Responses to Internal ^{137}Cs : A Model for a RDD

J.N. Finkelstein, C. Johnston, E. Hernady, C. Reed, S. Thurston, T. Morgan, R.A., Britten, J.P. Williams

Intracellular Decorporation of Pu/Am by Different Galenic Forms of Ca-DTPA

P. Fritsch, A.L. Sérandour, O. Grémy, G. Phan, N. Stapis, E. Fattal, H. Benech, J.R. Deverre and J.L. Poncy

Effects Of Incorporated Radionuclides On Hydrobionts Within The Chernobyl Accident Exclusion Zone

D.I. Gudkov, N.L. Shevtsova, E.V. Dzyubenko, A.B. Nazarov

Dissolution of Thorium and Uranium from a Therapeutic Soil in a Synthetic Gastrointestinal Fluid

V. Höllriegl, U. Oeh

Calculation And Assigning Of Internal Doses From Derivated Air Concentration (Dac) Of Radioactive Aerosols With Natural Uranium In Nuclear Fuel Plant -Pitesti

T. Ivana, Gh. Epure

Application of the Laser Spectroscopy for Actinides Trace Amount Detection and Valence States Determination

I.N. Izosimov

Study on the Administration Strategy of the Potassium Iodide (KI) in a Nuclear Emergency

M. Jang, K.D. Park

Analysis of the Variability of Biokinetic Model Parameters Due to Inter-Individual Variation

W. Klein, B. Breustedt, M. Urban

Biomaterials for Decorporation of Cobalt-60 in the Rat

T.G. Levitskaia, K.D. Thrall

Occupational Dose Assessment of Iodine Intake at ANSTO

H. Meriaty

Medical Procedure of a Cutaneous Contamination

X. Michel, P. Berard, F. Menetrier, P. Laroche

Radionuclide Decorporation Agent Advanced Development for Use in Radiological Public Health Emergencies: Roles of NIAID and BARDA, Running Title: Advanced Development for Radionuclide Decorporation Agents

B.R. Moyer, R.G. Manning, J.M. Prasher, K.D. Cliffer, A. Macaluso, W.S Young, B.W. Maidment, R.J. Hatchett

Evaluation of Chitosan for Uranium Decorporation in the Rat

J. Peterson, K. Thrall, T. Levitskaia

Tracy U: The French Cohort of Uranium Cycle Workers

E. Samson, I. Guseva Canu, A. Acker, D. Laurier, M. Tirmarche

Physiology of the Biokinetics of Plutonium, DTPA and Decorporation Therapy

J. Schimmelpfeng, B. Breustedt, M. Urban

Ingestion Of Ra-226 From Activated Paints On Military Equipment: Transfer Factors And Doses

A. Schirmer

Calixarene Nanoemulsion: A New Treatment for Uranium Skin Contamination

A. Spagnul, C. Bouvier-Capely, G. Phan, F. Rebière, E. Fattal

MEDICAL DECORporation Software to Assist First Responders, First Receivers and Medical Reach-Back Personnel in Triage, Treatment and Risk Assessment From Internalized Radionuclides

E. Waller

A Case-Control Study of Breast Cancer in Women Living Around Semipalatinsk Nuclear Test Site

T. Zhunussova, Y. Ishibashi, Y. Shibata, A. Masadykov, A. Liland

ABSTRACTS

Monday, May 11, 2009

EPIDEMIOLOGY ON INTERNALLY DEPOSITED RADIONUCLIDES, D. Melo, Chair

Life Span Study on Late Effects of Radium-224 in Children and Adults

H. Spiess

University Children's Hospital, 80336 Munich, Pettenkoferstr. 8a

Between 1945 and 1955, several thousand patients were injected with a preparation containing Radium-224 (Ra-224) called Peteosthor as treatment for bone tuberculosis or ankylosing spondylitis. Ra-224, like Plutonium-239, is a bone seeking nuclid. During the course of early experimental work it became clear 1948 that the short lived α -emitter Ra-224 becomes particularly concentrated in the growing zones of the bones. Consequently I gave a strong warning against the administration of Peteosthor, especially to patients in growing age, officially in 1950 at the German Congress of Orthopedics, and epidemiological investigations were initiated. Our study population comprises 899 persons (including 217 children or juveniles) who received injections of Ra-224. The study has now been conducted for a follow-up period of over 60 years.

The most striking detrimental health effect following Ra-224 injections are the 57 malignant bone tumors, occurring predominantly in childhood. This was the special reason for my invitation to the first conference on "Delayed Effects of Bone seeking Radionuclides" in Sun Valley, USA, in September 1967. This meeting was organized by our later friend and cooperator Charles Mays. I reported on 50 Ra-224 induced bone tumours in children and adults, growth disturbances, osteochondroma and cataracts, concluding that the younger the age at Ra-224 injection, the more severe the late effects.

Up to now 57 malignant bone tumors have been observed with a peak occurring 8 years after the first Ra-224 injection. The last case of bone sarcoma occurred 46 years after injection. A total of 270 non-skeletal malignant diseases were observed where 192 could be expected. Further details will be given in the paper by Nekolla et al., presented by Dr. Walsh.

In the past two years, on comparison of 124 study group members still living, to 166 living control persons with no exposure to Ra-224, an increase of non-cancer diseases has become apparent in the exposed group. The breakdown of these diseases is: kidney insufficiency, 21 study group members versus 3 controls where

8 study group members required dialysis versus 2 controls; thyroid (struma nodosa), 36 versus 29; heart-attack, 16 versus 4; coronary heart disease, 17 versus 8. This hypothesised increase of non-cancer diseases becomes more important in the description of radiation late effects, whereas the increased incidence rate of malignant diseases is slowing down.

Non-skeletal Malignant Diseases in Patients Treated with Radium-224

E.A. Nekolla¹⁾, L. Walsh¹⁾, H. Spiess²⁾

¹⁾ Federal Office for Radiation Protection, BfS, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany

²⁾ Children's Hospital, University of Munich

Several thousand German patients suffering from ankylosing spondylitis, tuberculosis and some other diseases, received multiple injections of the short-lived α -emitter ²²⁴Ra. The "Spiess study" was initiated in the early 1950s to follow the health of 899 persons (278 female, 621 male) who were treated mainly between 1945 and 1955. Most of the high dose patients and nearly all of those treated as children or juveniles (n=217) were included in the study. In December 2007, 124 persons were still alive. The most striking observed health effect, following ²²⁴Ra injections, was a temporal wave of 57 malignant bone tumours with a maximum at about 8 years after exposure which has already been described in several publications. During the two most recent observation decades, a significant excess of *non-skeletal* malignant diseases has become evident.

Materials and methods: The expected number of cases were computed from the age, gender and calendar year distribution of person years at risk and the gender, age and calendar year specific incidence rates from the German Saarland Cancer Registry. These were compared with the observed number of cases. A minimum latency (lag) period of 5 years for solid tumours was assumed. To test for statistical significance Poisson statistics were applied.

Results: As of December 2007, the total number of observed malignant non-skeletal diseases was 270 vs. 192 expected cases (248 specified cases of non-skeletal solid cancers, 22 other malignant diseases: 16 malignant neoplasms of lymphatic and hematopoietic tissue and 6 without specification of site). Accounting for a 5 years lag period and excluding 13 cases of non-melanoma skin cancer (mainly basalomas) 231 of non-skeletal solid cancers were observed vs. 151 expected cases. Significant increases of cancer rates were observed for several sites: for breast cancer (32 cases observed vs. 9.7 cases expected), soft tissue malignancies (11 vs. 1.0), thyroid carcinomas (7 vs. 1.0), liver (10 vs. 2.4), kidney (13 vs. 5.0), pancreas (9 vs. 4.1), bladder cancer (16 vs. 8.0), and cancer of female genital organs (15 vs. 7.8). The standardized incidence ratio of 7.5 for mammary cancers in those women exposed as children or juveniles is particularly striking; moreover, 2 cases of breast cancer occurred in men (vs. 0.25).

Radon And The Risk Of Cancer Mortality – Results From The German Uranium Miners Cohort.

Linda Walsh, Maria Schnelzer, Annemarie Tschense, Bernd Grosche & Michaela Kreuzer

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Extensive uranium extraction took place from 1946 until 1990 at the former Wismut mining company in East Germany. 58,987 former male employees form the largest single uranium miners cohort, which has been followed up for causes of mortality occurring from the beginning of 1946 to the end of 2003. The purpose of this paper is to present the radon exposure related cancer mortality risk based on 20,920 deaths, including 3,016 lung cancers and 3,340 extrapulmonary cancers and 2 million person years. Internal Poisson regression was used to estimate the excess relative risk (ERR) per unit of cumulative radon exposure in Working Level Months (WLM).

A clearly preferred ERR model for lung cancer is linear in radon exposure with exponential effect modifiers which depend on age at median exposure, time since median exposure and radon exposure rate. In this model the central estimate of ERR/WLM is 0.54% (95% CI: 0.40; 0.68) for an age at median exposure of 30 years, a time since median exposure of 20 years and an exposure rate of 3WL. This central ERR decreases by 5% for each unit exposure rate increase. The ERR decreases by 28% with each decade increase in age at median exposure and also decreases by 51% with each decade increase in time since median exposure. The simple cohort ERR/WLM for lung cancer is 0.19% (95% CI: 0.16; 0.21).

The ERR/WLM for all extrapulmonary cancers combined is 0.014 % (95% CI: 0.006 – 0.023 %). Most cancer sites showed an increased ERR/WLM, but these are either insignificant or become insignificant after adjustment for potential confounders such as arsenic or dust. The highest ERR/WLM is observed for cancers of the tongue/mouth (0.045 %), pharynx (0.163 %) and liver cancer (0.044 %). The present data provide some evidence of an increased risk of extrapulmonary cancers associated with radon, but chance and confounding cannot be ruled out.

Future work will involve the recomputation of the risks presented here with respect to organ doses, currently being quantified in the EU alpha-risk project. Data from the Wismut cohort study will soon be opened for interested scientists for further analysis. For more information please see www.bfs.de/de/bfs/forschung/wismut.html.

Leukaemia Risk Among Czech Uranium Miners In Dependence On Doses From Radon, External Gamma, And Long Lived Radionuclides

Ladislav Tomasek¹, Irena Malatova¹, James Marsh²

¹ National Radiation Protection Institute, Prague, Czech Republic

² Health Protection Agency, Radiation Protection Division, Chilton, Didcot, UK

The study presents recent findings based on leukaemia incidence in Czech uranium miners. Information on causes of death were obtained from death registries and data on notified cases were drawn from compensation claim files. Control subjects were selected from two large cohort studies which covered exposure in uranium miners in years 1948-63 and 1968-88. The controls were matched to cases according to the sub-cohorts, birth year, and attained age. The risk is analyzed in relation to cumulated equivalent dose from radon and its progeny, external gamma radiation and inhaled long lived alpha radionuclides. Exposures were estimated from extensive radon measurements since 1949, from measurements of external gamma radiation since the early 1960s and measurements of gross alpha activity in the aerosol since the 1970s. The earlier exposures were estimated from uranium content in the ore and from aerosol measurements in mines.

The annual absorbed doses to the red bone marrow dose has been calculated for each miner from the first year of employment to the year of diagnosis of the case. The dose calculated rising from exposure to radon gas, radon progeny, long lived radionuclides in the uranium ore dust and from exposure to external gamma. The dosimetric and biokinetic models developed by ICRP has been used in the calculations. The mean cumulated equivalent dose in the present study is 193 mSv. About 42% of the total dose is due to inhalation of uranium and its decay products, about 30% is due to gamma radiation, and 28% of the dose is from radon and its progeny.

The risk coefficient (excess relative risk per sievert) corresponding to the above dose estimates is 4.0 (95%CI: 0.1 – 10.6). The estimated risk is subject to some uncertainty due to small numbers and the uncertainty in the estimated dose. However, the magnitude of the risk is consistent with estimates from other studies.

The present work was supported by the State Office for Nuclear Safety of the Czech Republic (VZ 60022490) and by the European Commission under FP6 (Contract FI6R 516483).

Preliminary Lung Cancer Risk Assessment Of Exposure To Radon Progeny For Transylvania, Romania

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²University of Salzburg, Division of Physics and Biophysics, Salzburg, Austria

At the beginning of the 1950s, exposure to radon and its progeny in mines was identified as a major risk of lung cancer, but only since the 1970s it has been recognized as a major source of natural exposure and, implicitly, health concern to the general public.

The objective of the present study was to assess the lung cancer risk induced by exposures to radon progeny of people living in some areas of Transylvania. Indoor radon concentrations were measured in 716 dwellings of Cluj, Bihor, Bistrita and Sibiu-Alba counties. Measurements were performed using CR-39 track detectors, exposed for a minimum of 3 months. Average indoor radon concentrations were 120, 129, 69 and 87 Bq/m³ for Cluj, Bihor, Bistrita and Sibiu-Alba, respectively. Measured radon and radon progeny concentrations were converted into exposure and then into absorbed dose in order to establish a dose-effect relationship and hence lifetime lung cancer risks for these populations.

First, a stochastic dosimetry model was used to relate exposure to cellular dose. Then a biologically-based Initiation-Promotion carcinogenesis model (from dose to cancer risk), based on experimentally observed cellular transformation and survival functions, was applied to model the sequence of events from dose to lung cancer induction. Random alpha particle intersections of bronchial cells during a given exposure period were selected from a Poisson distribution. For continuous low-level exposures, it was assumed that cancer induction is related to the cycle time of an irradiated cell, thus exhibiting a distinct dose-rate effect. The dominant role of single hits leads to a linear dose-response relationship at low radon exposure levels.

The biologically based mechanistic model proposed for assessing the lung cancer risk and dose-effect relationship induced by indoor radon exposure indicated excellent agreement between the theoretically predicted risk and other epidemiologically observed relative risks, confirming its validity. This enabled us to apply this Initiation-Promotion model to the assessment of the lung cancer risk induced by exposure to radon progeny for people living in some regions of Transylvania, permitting a comparison between these estimates and the ones reported for Europe. The predicted relative risk was about 1.07 for the investigated counties from Transylvania.

Site-Specific Cancer Risk And Occupational Exposure To Uranium

Irina Guseva Canu¹, Sophie Jacob¹, Elisabeth Cardis⁴, Pascal Wild², Sylvaine Caër-Lorho¹, Bernard Auriol³, Alain Acker³, Dominique Laurier¹, Margot Tirmarche¹

¹Institut de Radioprotection et de Sûreté Nucléaire, ²Institut National de Recherche en Sécurité, ³AREVA NC ; France, ⁴CREAL, Spain

Objective: To investigate the risk of site-specific cancer mortality in relation to occupational exposure to uranium.

Methods: A cohort of 2709 male workers (72786 person-years) employed at the AREVA NC uranium processing plant (1960-2005) in France was constructed. Cause-specific mortality in the cohort was compared to that of the French population for the period 1968-2005 by computing standardized mortality ratios. Exposure to different uranium compounds, classified by their solubility type, was assessed on the basis of the plant specific job-exposure matrix. Internal comparison between exposed and unexposed subjects was then carried to estimate relative risk (RR) of site-specific cancer death in regards of each type of exposure. Based on the potential uranium target organs (lung, kidney, bone, upper aero-digestive tract, and lymphatic and haematopoietic tissue) we considered specific cancers for which at least 10 deaths were observed. Cox proportional hazard model with adjustment for attained age, calendar period and socioeconomic status was used for analyses.

Results: At the end of the follow-up, 48 deaths from lung cancer, 26 deaths from upper aero-digestive tract cancer, and 18 deaths from lymphatic and haematopoietic tissue cancer were observed. For none of these causes, mortality among the cohort was significantly increased comparatively to the national mortality. Internal comparison showed an elevated risk of lymphatic and haematopoietic tissue cancer among workers exposed to slowly soluble reprocessed uranium-bearing compounds (RR=5.5; 95%CI: 1.3-22.6). On the whole, for the lung cancer and the lymphatic and haematopoietic tissue cancer mortality risk tended to increase with decreasing solubility of reprocessed uranium compounds. Nevertheless, only one increased RR associated with exposure reached statistical significance (p<0.05).

Conclusion: Even though statistical power of analyses was limited, our findings are consistent with data from experimental studies of biokinetic and action mechanism of slowly soluble uranium oxides. Moreover, two epidemiological studies reported a positive association between lymphatic and haematopoietic cancer and uranium internal dose. At this stage, too few cancer deaths were observed for carrying more detailed dose-effect analyses. Extension of this cohort to other plants and its longer follow-up should allow more powerful analyses to confirm these findings and to investigate effects of protracted uranium exposure on specific cancer mortality.

Occupational And Medical Exposure To Ionizing Radiation And Leukemia Risk Among German Uranium Miners

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Background: Lung cancer is a well known effect on uranium miner's health from exposure to radon. But little is known about the effect of ionizing radiation on other cancer entities in miners. Moreover, a study recently carried out in radiation workers has shown that routine occupational X-ray examinations can result in a significant fraction of the total absorbed dose (Daniels et al., 2005). Therefore, the aim of the present study was to reexamine leukemia risk among miners, taking into account also the exposure due to routine X-ray examinations, which were performed to detect tuberculosis and silicosis as early as possible.

Methods: Data from a previously analyzed individually matched case-control study of former uranium miners in East Germany with 377 cases and 980 controls were used (Möhner et al., 2006). Additionally, data about X-ray examinations were abstracted from medical records for most of all subjects. Moreover, absorbed dose from the occupational radiation exposure was estimated using recently developed software (Marsh et al., 2008).

Results: Absorbed dose to red bone marrow due to occupational exposure was slightly higher in cases than in controls (mean: 26.3 mGy vs. 22.5 mGy). The absorbed dose from diagnostic uses of radiation was even a little higher (mean: 27.1 mGy in cases and 25.3 mGy in controls). Using conditional logistic regression models, a moderately but not statistically significant elevated risk was seen in the dose category above 200 mGy for the combined dose from both sources (OR=1.52, 90%-CI:[0.95 – 2.44]). Ignoring the dose accumulated in the recent 20 years the risk in the highest dose category (>60 mGy) is even higher (OR=2.64, 90%-CI:[1.61 – 4.35]). In contrast, taking into account only dose accumulated over the recent 10 years no risk increase is observed with increasing dose. The use of silicosis as a surrogate measure yielded, that miners who suffer from silicosis for more than 15 years, have a more than twice as high risk of falling ill with leukemia than other miners.

Conclusions: The results suggest that leukemia risk is influenced not only by recent exposures to ionizing radiation. Moreover, exposure to medical X-ray, especially Chest-X-ray does not seem to be negligible in the discussion about leukemia risk. Part of this work was funded by the EC under contracts 516483 (FIP6).

Early Effects in Haemopoiesis in Chronic Radiation Exposure of People

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Objectives: Hematopoiesis is the most radiosensitive system. The major goal of this study is to reveal and quantitatively describe the regularities between the characteristics of chronic exposure to ionizing radiation and the specific patterns of hematopoietic inhibition.

Methods: In this study, we used 22,000 hemograms for more than 8,500 individuals and results of bone marrow aspirates for 529 individuals from the unique internationally-recognized Extended Techa River Cohort. Mean cumulative red bone marrow (RBM) dose was 354.6±3.99 mGy. Statistical methods include empirical analyses of frequencies of cytopenic states of investigated blood lines (e.g. leukocyte, neutrophile, platelets, erythrocyte, etc.) and regression methods included generalized linear models and logistic regressions which allowed for taking into account the health states representing by ICD-9 codes. **Results:** Data analysis showed gradual increase of frequency of cytopenias with growing of the dose rate value in peripheral blood, the increase of total cellularity or RBM, the number of erythrokaryocytes (especially immature forms), and plasma cells as well as the decline in myeloid to erythroid ratio with the maturation arrest in granulocytic line and significant decline in the numbers of lymphocytes and monocytes. Quantified association of dose characteristics with patterns of hematopoiesis inhibition are found to be essential. The pattern of dose characteristics better predicting the hematopoiesis response is identified for each blood line. The background contribution of diseases possible influencing blood counts is calculated. Nonlinear dose and age effects are estimated. The concept of two-fold increase dose rate is elaborated and its estimates are done for a spectrum of subpopulations. **Conclusion:** Chronic exposure to ionizing radiation results in an increase in damages of cells in RBM leading to elimination of cells or their growth arrest which in turn results in compensatory stimulating proliferation activity which in turn results in compensatory stimulating proliferation activity which is observed as an increase of the amount of myelokaryocytes, deceleration of maturation, and elimination of defective cells in RBM which can result in a decrease of cellularity in peripheral blood at normal cellularity or even hyperplasia of RBM.

BIOLOGICAL EFFECTS OF INTERNALLY DEPOSITED RADIONUCLIDES, B. Boecker, Chair

Toxicity Of Alpha-Emitting Radionuclides: From Curie To Litvinenko

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Marie Curie discovered polonium and radium in 1898 and died of aplastic anaemia or leukaemia in 1934. At the time, the toxic effects of ionizing radiation were poorly understood. A century later, a lot more is known of the carcinogenic properties of radiation and its ability to cause gross tissue damage and death at high doses. A striking recent example of radionuclide toxicity was the death in 2006 of Alexander Litvinenko, thought to have been due to the ingestion of polonium-210. Haemopoietic bone marrow is the target tissue for the induction of leukaemia and bone marrow syndrome is a critical component of the acute effects of high dose radiation. Alpha-emitting radionuclides differ in their toxicity in terms of their ability to cause leukaemia and destruction of haemopoietic marrow, depending on their distribution and retention within the skeleton. Thus, epidemiological studies have shown that bone-seeking alpha-emitting radionuclides, including radium isotopes and plutonium-239, are poor leukaemogens. However, excess leukaemia was observed in patients given the thorium-232 oxide preparation, Thorotrast, injected intravascularly as a contrast agent, although comparisons with risk factors derived for exposure to external gamma rays suggest a low alpha particle RBE for Thorotrast induced leukaemia. Since Thorotrast distributes throughout active marrow, while bone-seeking alpha emitters irradiate only peripheral marrow close to bone surfaces, it is possible that target cells for leukaemia induction are located away from bone surfaces. However, stem cell populations are located close to bone surfaces as well as in more central locations, suggesting that those near bone surfaces may be more sensitive to cell killing or may not be the primary target for induction of leukaemia. Since polonium-210, like Thorotrast, distributes throughout bone marrow, it is also likely to be a more effective leukaemogen than bone-seeking alpha-emitting radionuclides, as well as having the potential to destroy all haemopoietic activity at high doses.

This paper will examine the development of our knowledge of the toxicity of alpha particle irradiation with particular reference to irradiation of bone marrow and our growing understanding of stem cell location and function. More generally, the toxicity of different radionuclides will be compared in terms of their carcinogenic potential and their ability to destroy tissue function.

Long-Term Cellular Effects In Humans Chronically Exposed To Ionizing Radiation.

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The aim of the study was to assess the frequency of chromosome aberrations/mutations and peculiarities of intracellular processes responsible for protection of cells against damage at late time after onset of exposure. The study group comprised of 692 individuals chronically exposed to radiation (the mean cumulative dose was 0.62 Gy) due to production activities at the Mayak NF, (The Southern Urals, Russia) and 338 unexposed individuals.

Study subjects who had manifested hemopoiesis inhibition (e.g., leucopenia) and/or with diagnosed chronic radiation syndrome (CRS) during the early period of exposure (at the time of the highest dose rates) were noted to have an increased frequency of micronuclei, dicentric chromosomes, mutations in the Tp53 gene, somatic mutations (CD3-CD4+ cells). In exposed persons without cytopenia and/or CRS, the intensity of mutational processes at a late time after the exposure was found to be at the background level.

Exposed individuals with leucopenia exhibited a lower Cu/Zn-SOD concentration ($137.1 \pm 21.3 \text{ ng/ml}$) as compared to exposed individuals without leucopenia ($189.9 \pm 13.9 \text{ ng/ml}$, $p=0.07$). In comparison with unexposed subjects ($42.8 \pm 1.8 \mu\text{mole/l}$), a significantly increased concentration of nitric oxide ($63.4 \pm 6.1 \mu\text{mole/l}$, $p<0.0001$) was noted in these patients. No significant changes in the repair activity were observed in the exposed versus the unexposed group. The number of persons with increased reference values for apoptosis frequency was found to be higher among CRS patients (21.6% vs. 9.1% in the control group), while it was unchanged among the remainder exposed (11.1%) versus unexposed subjects. In the total of exposed individuals, the number of cells with delayed cell cycles (based on Chk-2 concentration) was found to be increased ($0.8 \pm 0.22\%$) in comparison with that shown by unexposed subjects (0.3 ± 0.06 , $p=0.05$), however, the phenomenon was not registered in CRS patients ($0.4 \pm 0.12\%$).

Thus, the state of the cell's functional mechanisms responsible for maintenance of the body's genetic homeostasis at late time after the onset of exposure can be described as an adaptively-activated one. Subjects with early effects manifested by the hemopoietic system (cytopenia, CRS) demonstrated a significant increase in the frequency of cell mutations/aberrations at later time which obviously resulted from a highly probable functional disturbance of intracellular protection mechanisms.

Long Incubation Period From The Induction Of Cancer By Thorotrast Is Attributed To The Uneven Irradiation Of Hepatocytes At The Microscopic Level

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Irradiation from internally deposited radionuclides induces malignant tumors. Ingested radionuclides accumulate in specific organs which are irradiated over a life long period. Our aim is to elucidate why the development of malignant tumors requires long-term internal exposure, the order of decades, despite the fact that irradiation is continuous over this period.

We analyzed the most relevant cases to cancers induced by internal exposure, intrahepatic cholangiocarcinoma in Thorotrast patients (Th-ICC). Autoradiography showed that the density of alpha tracks was 50 times more concentrated than would be expected if Thorotrast were evenly distributed throughout the liver. The age-incidence curve revealed the incidence of hepatobiliary cancer in Japan increased in proportion to the 7th power of age whilst that of Th-ICC to the 6th power. Internal radiation significantly increased the randomness of hepatocyte distribution but not the density. Three major factors are considered to be responsible for the long incubation time: uneven distribution of radionuclides, limited range of irradiation and dynamic movement of tumor precursor cells. Target cells susceptible to malignant transformation may undergo one event and may then migrate outside of the range of alpha-particles, thereby avoiding immediate induction of successive additional events that would lead to cell death or neoplastic changes.

Late-Occurring Pulmonary Pathologies Following Inhalation Of Mixed Oxide (U,PuO₂) Aerosol In The Rat.

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Exposure to alpha-emitting particles is a potential long-term health risk to workers in nuclear fuel fabrication plants. Mixed Oxide (MOX: U,PuO₂) fuels containing low percentages of plutonium (Pu) obtained from spent nuclear fuels and surplus weapon-grade Pu are increasingly employed. Accidental contamination by inhalation may result in the development of late-occurring pathologies such as lung cancer. However, long term risks with regard to lung cancer are to date unclear. For MOX fuels, the risk may be different from that assigned to the individual components (Pu, U) given different physico-chemical characteristics. The objective of this study was to investigate late effects in rat lungs following inhalation of MOX aerosols of similar particle size containing 2.5 or 7.1% Pu.

Conscious rats were exposed to MOX aerosols using a "nose-only" system and kept for their entire life span. Different Initial Lung Deposits (ILDs) were obtained using different concentrations of the MOX suspension. Lung total alpha activity was determined by external counting and at autopsy for total lung dose calculation. Anatomic-pathological, autoradiographical and immunohistochemical analyses were performed on fixed lung tissue to determine the nature and frequencies of lung pathologies.

Inhalation of MOX at ILDs ranging from 1-20 kBq resulted in lung pathologies (90% of rats) including fibrosis (70%) and malignant lung tumours (45%). At higher ILDs (4-20 kBq) survival time was reduced (N=103; p<0.05) and frequently associated with lung fibrosis and emphysema. Multiple lung pathologies and metastases were observed in 17% and 13% of rats respectively. Malignant tumour incidence (adenocarcinoma, squamous, adenosquamous cell carcinoma) increased in a linear manner with dose (up to 60 Gy) with a risk of 1-1.6% Gy⁻¹ for MOX, similar to reported data for industrial PuO₂ alone (1.9 % Gy⁻¹). The appearance and risk of tumour development was independent of different Pu content. Immunolabelling with anti-Surfactant Protein C, anti-Thyroid Transcription Factor1 or anti-Oct4 antibodies showed differential staining of the various tumour types that proved a useful adjunct for tumour diagnosis.

In conclusion, late effects following MOX inhalation result in similar risk for development of lung tumours as compared with industrial PuO₂. At high doses deterministic effects prevail, resulting in lung fibrosis and decreased life-span.

Financial support from AREVA-NC and CEA is gratefully acknowledged.

Carcinogenesis From Inhaled $^{239}\text{PuO}_2$ In Beagles: Evidence For Radiation Homeostasis At Low Doses ?

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Background. From the early 1970s to the late 1980s, Pacific Northwest National Laboratory conducted life-span studies in beagle dogs on the biological effects of inhaled plutonium ($^{239}\text{PuO}_2$, $^{238}\text{PuO}_2$, and $^{239}\text{Pu}[\text{NO}_3]_4$) to help predict risks associated with accidental intakes in workers. Years later, the purpose of this study was to reassess the dose-response relationship for lung cancer induction in the $^{239}\text{PuO}_2$ dogs compared to controls. **Methods.** $^{239}\text{PuO}_2$ aerosol (2.3 μm AMAD, 1.9 μm GSD) was administered to six groups of 20 young (18-month old) beagle dogs (10 males and 10 females) by inhalation at six different activity levels, as previously described in Laboratory reports. Control dogs were sham-exposed. In dose level 1, initial pulmonary lung depositions were 3.5 ± 1.3 nCi (130 ± 48 Bq), corresponding to 0.029 ± 0.001 nCi/g (1 Bq/g) lung tissue. Groups 2 through 6 received initial lung depositions (mean values) of 22, 79, 300, 1100, and 5800 nCi $^{239}\text{PuO}_2$, respectively. For each dog, the absorbed dose to lungs was calculated from the initial lung burden and the final lung burden at time of death, and known lung mass, assuming a single, long-term retention function. For dogs with lung tumors, the lifetime absorbed dose was also calculated to 12 months prior to observation of a lung tumor to correct for an assumed 12-month latent period. **Results.** Insoluble plutonium oxide exhibited long retention times in the lungs. Increased (dose-dependent) mortality due to lung cancer (bronchiolar-alveolar carcinoma, adenocarcinoma, epidermoid carcinoma) and radiation pneumonitis (highest exposures group) was observed in dogs exposed to $^{239}\text{PuO}_2$. Calculated lung doses ranged from a few cGy in early-sacrificed dogs to 7800 cGy in dogs that died of radiation pneumonitis. Dog data were regrouped by lifetime lung dose and plotted as a function of lung tumor incidence. Lung tumor incidence in controls was 16% (4/25). However, no lung tumors were observed in 33 dogs with the lowest lung doses (8 to 70 cGy, mean 39 ± 31 cGy), and only three lung tumors were observed in 19 dogs with lung doses ranging from 136 to 254 cGy (mean 195 ± 59 cGy). **Conclusion.** The overall slope of the dose-response function was 435 tumors/ $10^6 \cdot \text{dog} \cdot \text{cGy}$. The incidence of lung tumors in controls ($n = 25$) was significantly different than in the lowest-exposure group ($n = 33$), at the $p < 0.01$ confidence level, suggesting a marked protective effect (radiation homeostasis) of alpha-particle radiation at low doses from $^{239}\text{PuO}_2$.

The RBE For Lung Cancer In Rats

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The stochastic effects in the lung of inhaled, insoluble particles of α - and β -emitting particles and low-LET thoracic irradiation were compared in rats using data from previously conducted studies. Male and female F344 rats were exposed briefly by nasal inhalation to relatively insoluble aerosols of $^{239}\text{PuO}_2$ or $^{144}\text{CeO}_2$ to achieve a range of four lung burdens. The mean lifetime β doses to the lung were 3.6 ± 1.3 Gy, 6.8 ± 1.7 Gy, 12 ± 4.5 Gy and 37 ± 5.9 Gy. The mean lifetime α doses to the lung were 0.06 ± 0.03 Gy, 0.95 ± 0.46 Gy, 3.7 ± 1.6 Gy and 12 ± 2.4 Gy. Additional rats were exposed to fractionated thoracic doses of X-rays; one-tenth of the total exposure given on ten successive working days and observed for their life span. The absorbed doses to the lung were 3.6 ± 1.3 Gy, 6.8 ± 1.7 Gy, 12 ± 4.5 Gy and 37 ± 5.9 Gy. Appropriate sham controls were included in each group and all groups were observed for their life spans.

Lung neoplasms were found in all groups of rats, with the incidence increasing with radiation dose. Rats exposed to $^{239}\text{PuO}_2$ had the highest incidence, 94% in the group with a dose of 12 Gy. The incidence was similar in the groups exposed to inhaled $^{144}\text{CeO}_2$ or thoracic X-irradiation. The incidence of lung tumors in the $^{239}\text{PuO}_2$ groups was 10 to 20 times higher than that of the groups exposed to the low LET radiations. These results support an RBE of 20 as recommended by ICRP 60.

*Deceased

Measurements Of The Relative Toxicity Of ²⁴²Cm Alpha- And ⁴⁵Ca Beta-Radiations In Mice.

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Relative biological effectiveness (RBE) and relative toxicity (RT) are both valid measures of the effectiveness of a given radiation type in producing biological damage relative to that produced by a referent radiation type – commonly a whole-body exposure to a low LET X- or gamma-rays. Consequently, these terms are often treated as interchangeable – such that both have been used to derive radiation-weighting factors (W_R) for dosimetry. While RBE and RT are equivalent when the dose-response for both radiation types is linear they are not when other dose-response relationships are found. Moreover, under some circumstances experimental data can generate two possible RBE values and under other circumstances RBE values can either approach or be infinite. Under these circumstances measured RT values are more meaningful. The paper will use the results of two studies comparing the toxicity of ⁴⁵Ca beta-particles and ²⁴²Cm alpha-particles in mice to demonstrate the effect of dose-response relationship on the measured values of RBE and RT. The results of this study will also be used to demonstrate the considerable variability in the RT of alpha-particles cf. beta-particles as a function of tumour type.

Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission of Genetic Damage and Transgenerational Offspring Effects.

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The Persian Gulf War resulted in a number of casualties among U.S. personnel (male) injured by fragments from depleted uranium (DU) munitions. While there have been no acute adverse offspring effects resulting from paternal DU exposure (twenty pregnancies), it is unknown whether these embedded fragments will affect the long-term health of the children conceived by these soldiers. Animal studies have demonstrated that paternal preconceptional exposure to radiation or heavy metals like cadmium can induce cancer in unexposed offspring. To address this question, we investigated the paternal transmission of genetic damage in offspring of male rodents carrying embedded DU fragments using a transgenic mouse model. This system allows us to assess *lacI* gene mutation frequency in multiple tissues obtained from progeny of exposed fathers by employing a *lacI* shuttle vector carried by cells of a transgenic mouse (Big Blue: strain C57BL/6 hemizygous mice containing 40 copies of a *lacI* shuttle vector per cell). Male rodents were internally exposed to DU (high and low dose) and the mutation frequencies in testes and bone marrow were then measured. Offspring from exposed male parents were genotyped and those positive for the *lacI* gene were assessed for transmission of genetic damage in bone marrow tissue. Data demonstrate that DU exposure (high and low dose) induced a significant increase in the *lacI* mutation frequency in both testes and bone marrow (10.2- and 6.5 fold elevation respectively). Offspring from DU-exposed (high dose) male parents also demonstrated a significant increase in the mutation frequency of the *lacI* gene in their bone marrow (9.4-fold elevation). The mutation frequency in bone marrow from progeny of males exposed to a lower dose of internalized DU was not significantly different from control (nonsurgical and Tantalum-implanted P1) progeny. Progeny from neutron exposed fathers also showed an increase in bone marrow *lacI* mutation frequency while progeny from unimplanted fathers did not demonstrate an increase in bone marrow mutation frequency. The results from this study indicate the possibility of transmission of genomic instability from male parents carrying embedded DU to the somatic cells of their offspring. Further studies are warranted.

Tuesday, May 12, 2009

DECORPORATION OF INTERNALLY DEPOSITED RADIONUCLIDES, N. Priest, Chair

Cuprimine[®] and Syprine[®], FDA-approved Therapeutics for Wilson Disease, are Promising Candidates to Decorporate the High-Energy Radioisotopes Cobalt-60 and Polonium-210.

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The risk of accidental or deliberate exposure of the populace to radionuclides prompts an urgent need for improved methods to remove internalized radioisotopes. Cuprimine (D-penicillamine) and Syprine (trientine) are therapeutics approved by FDA since 1963 and 1985, respectively, to treat Wilson Disease (a genetic defect in copper transport, leading to copper overload) by chelation and accelerated excretion of internally deposited copper. Literature suggests Cuprimine also decorporates lead, mercury, cobalt, bismuth, nickel, gold, arsenic and zinc. Syprine may remove iron, zinc, nickel, cadmium and manganese. We tested these agents in rats to confirm effectiveness of Cuprimine and test Syprine for cobalt-60, and to investigate them both as countermeasures against polonium-210, which was recently employed in a stealth assassination. Groups of animals received a single intravenous dose of either cobalt-60 or polonium-210. Cobalt-treated animals were immediately given a single oral dose of test drug targeted at 15 mg/kg; polonium-treated animals were dosed daily for five doses. Excreta were collected daily. Animals were sacrificed at 48h (cobalt) or 120h (polonium) after radionuclide administration. Blood and select tissues were collected at sacrifice, weighed and analyzed for radioactivity. For animals exposed to cobalt-60 and treated with a single oral dose of Cuprimine, statistically significant reductions in radioactivity in skeleton, kidney, liver, muscle and stomach were observed; reductions ranged from 39% for muscle to 56% for kidney. Syprine treatment was also effective at decreasing cobalt-60 in skeleton, with a statistically significant 35% reduction in administered dose. Interestingly, Syprine significantly elevated blood levels of cobalt-60, and increased urinary excretion of cobalt-60, emulating its behavior on copper. Repeat Cuprimine treatment over a 5-day period was effective at reducing spleen levels of polonium-210, although kidney radioactivity increased concomitantly. Syprine statistically significantly reduced polonium-210 in the spleen and skeletal tissues. In contrast to the control and Syprine treated groups, animals treated with Cuprimine showed no reduction in spleen weight as a percentage of body weight, perhaps due to protection against polonium-210 radiation-induced atrophy. Future studies should include histopathology evaluations to confirm these observations. These promising results should encourage further study of both agents, whose established safety and commercial availability can permit rapid deployment as countermeasures.

Alginate Reduces the Absorption and Retention of Ingested Strontium in the Rat

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Although four stable isotopes of strontium occur naturally, strontium-90 is produced by nuclear fission and is present in surface soil around the world as a result of fallout from past atmospheric nuclear weapons tests. It can easily transfer to man in the event of nuclear/radiological emergency or through the plant-animal-human food chain causing long-term population exposure. Strontium is chemically and biologically similar to calcium, and is incorporated primarily into bone following internal deposition. Alginic acid obtained from seaweed (kelp) extract appears to block systemic uptake of ingested strontium and reduce strontium distribution to bone in rats, while other natural polysaccharides including chitosan and hyaluronic acid had little *in vivo* affinity for strontium. Alginate exhibits the unique ability to discriminate between strontium and calcium and has been previously shown to reduce intestinal absorption and skeletal retention of strontium without changing calcium metabolism. In our studies, the effect of the alginate polysaccharide structure on strontium intestinal absorption was examined. Alginate composed of mixed linear polymeric molecules of D-mannuronic acid exhibited superior performance compared to one enriched in L-guluronic acid. One problem associated with alginate treatment is its limited solubility and gel formation in water. The aqueous solubility of sodium alginate was improved in a sodium chloride/sodium bicarbonate electrolyte solution containing low molecular weight polyethylene glycol (PEG). Furthermore, oral administration of the combined sodium alginate/PEG-600 solution synergistically accelerated removal of internal strontium in rats when compared to treatment with individual sodium alginate or PEG-600 solutions. Importantly, both alginic acid and PEG are nontoxic, readily available materials that can be easily administered orally in case of a national emergency when potentially large numbers of the population may require medical treatment for internal depositions. Our results suggest further studies to optimize *in vivo* decorporation performance of engineered alginate material via modification of its chemical and physicochemical properties is warranted.

Will Alteration Of Radiostrontium Biodistribution By Chlorthalidone Improve Therapy Of Painful Bone Metastases?

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Strontium-89 chloride in aqueous solution (Metastron™; FDA approved; single dose of 148 MBq) is injected intravenously for pain relief in patients suffering metastases of prostate and breast cancer. Speculation exists about mechanisms responsible for the pain palliation that lasts up to six months. Renal clearance of bone seeking Sr-89 (radioactive half-life 50.5 days) in humans is the main factor determining total-body Sr-89 retention for up to six days post-injection. An inverse relationship exists between the magnitude of total Sr-89 excretion and the extent plus severity of existing osteoblastic lesions. That therapy, however, is far from ideal. My earlier attempts (in 1969) employed several individual diuretics to enhance excretion of injected Sr-85 from normal laboratory rats. The studies revealed that only the monosulfamyl diuretic chlorthalidone prolonged Sr-85 whole-body retention through reduced renal excretion of radionuclide compared with that in controls. Fecal excretion of Sr-85 was unaffected. The other diuretics tested either negligibly increased Sr-85 excretion or had no effect. Today, FDA approved chlorthalidone is employed clinically to prevent formation of calcium kidney stones by decreasing calcium excretion in urine. Metabolism of alkaline earth elements calcium and strontium in humans is similar, but not identical. A PubMed literature review revealed no report of chlorthalidone tested to alter Sr-89 biodistribution in humans or experimental animals. In order to improve pain therapy, I suggest administering chlorthalidone USP (25 mg) orally daily to the patient, beginning three days prior to Sr-89 injection (to establish therapeutic chlorthalidone blood levels), on the day of injection, and for two weeks after injection. Bremsstrahlung scintigraphy of the patient by gamma camera from injected Sr-89 may yield a gross display of radionuclide biodistribution long after injection. Successfully prolonging whole-body Sr-89 retention with chlorthalidone would achieve the following: (1) Allowing a lower administered radioactivity dose achieving the intended therapeutic radiation dose to bone lesions through in vivo “recycling” of Sr-89 that would usually be excreted, (2) Achieving a longer period of lesion irradiation from the deposited Sr-89 bone dose which may elicit greater and longer pain relief, (3) Reducing residential and sewage contamination from patients discharged home after therapy, and (4) Reducing environmental Sr-89 contamination by confining more dosed radionuclide within the cadaver of patients dying from their metastatic disease.

¹³⁷Cs Dose Reduction Due to Prussian Blue

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Prussian Blue (PB) is an efficient drug for enhancing cesium elimination from the body. PB was administered in dosages of 3, 6 and 10 gd⁻¹ for adults internally contaminated in the 1987 Goiania accident, in Brazil. Children were given 1 to 3 gd⁻¹. PB treatment started at the earliest 10 days after intake. The clearance of cesium after PB administration was independent of age, sex and administered dose, in the range of 3 to 10 gd⁻¹. To complement the data from Goiania, ¹³⁷Cs was injected in 6 pairs of beagle dogs, of 3 different ages. PB was available in the drinking water of three pairs of dogs. The retention of cesium in the body through the action of PB was similar for dogs and humans. For humans it may be mathematically represented by the sum of two exponential terms, a fast clearance term (half-life of 2-3 days) and a long clearance term (half life of 26 days), for all age groups. The fraction of initial activity which is eliminated rapidly is higher for youngsters (0.5) than for adults (0.3). This model for ¹³⁷Cs internal contamination under influence of Prussian Blue was applied for a 10-y old reference child and for an adult male. If the drug is administered immediately after the intake, the committed dose coefficient is reduced by a factor of 2.4 for a 10-y old child (from 1.01E-08 to 4.29E-09 Gy Bq⁻¹). If the drug is given a few days after the intake the dose coefficient is reduced by a factor of 1.7 (from 1.01E-08 to 5.82E-09 GyBq⁻¹). For adults, if the drug is administered immediately after the intake, the effective dose coefficient is reduced by a factor of 4.2 (from 1.36E-08 to 3.23E-09 GyBq⁻¹). If the drug is given a few days after the intake the dose coefficient is reduced by a factor of 3.8 (from 1.36E-08 to 3.55E-09 GyBq⁻¹). These results show that PB is more efficient in adults compared to children. However, PB contributes to an important reduction on the children's doses, if administered immediately after the cesium intake.

***In Vitro* and *In Vivo* Evaluation of a Novel Decorporation Agent (SAMMS™) for Cesium (Cs) in Rats**

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Novel decorporation agents are being developed to protect against radiological terrorist attacks (i.e. dirty bombs). Nano-engineered solid sorbents for chelation therapy were developed and validated. These sorbents, known as the self-assembled monolayer on mesoporous supports (SAMMS™), are hybrid materials where differing organic moieties are grafted onto mesoporous silica (SiO₂). *In vitro* batch contact experiments focused on the evaluation, and optimization of SAMMS for capturing single and multiple radionuclides. In these experiments a number of parameters were evaluated including: sorption affinity (*K_d*), kinetics, selectivity and stability. Based on these studies, a copper ferrocyanide (Cu-FC-EDA)-SAMMS was advanced for *in vivo* evaluation for cesium (Cs) decorporation. *In vivo* experiments were conducted comparing the performance of the SAMMS vs. insoluble Prussian Blue, which is currently FDA-approved for Cs decorporation. Three groups of jugular cannulated rats (4/treatment) were evaluated. Group I was administered Cs (~40 µgeq/kg) by intravenous (iv) injection and oral gavage; Group II administered prebound SAMMS+Cs by oral gavage; and Group III evaluated orally administered Cs (~0.06 µgeq/kg) followed by 0.1 g of either SAMMS or Prussian Blue. Following dosing the rats were maintained in metabolism cages for 72 hr and blood, urine and fecal samples were collected for Cs analysis (gamma counting). Rats were then humanely euthanized, and liver, stomach, small and large intestine were analyzed. Orally administered Cs was well absorbed (~100% relative to iv dose), and the pharmacokinetics (blood, urine, feces & tissues) were very comparable to the iv dose group. For both exposures the urine and feces accounted for 20 and 3% of the dose, respectively. The prebound SAMMS+Cs was retained primarily within the feces (72% of the dose), with ~1.4% detected in the urine, suggesting that the Cs remained tightly bound to SAMMS, and is extensively eliminated in the feces. SAMMS & Prussian Blue both effectively chelated available Cs in the gut with feces accounting for 80-88% of the administered dose, while less than 2% was detected in the urine. This study suggests that the functionalized SAMMS provides comparable *in vivo* chelation efficacy with Prussian Blue. Future studies will focus on *in vivo* SAMMS chelation for complex mixture at higher doses of radionuclides. (Supported by NIH/NIAID grant R01 AI0 74064-01)

Review Of Recent Developments And Results In The Field Of Radionuclide Decorporation

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In case of accidental release of radionuclides in a nuclear facility or in the environment, or in the field of nuclear/radiological terrorism, internal contamination by either acute or chronic exposure has the potential to induce both radiological and chemical toxicity. Whatever the contamination route (inhalation, ingestion or wound), the radionuclide is absorbed, and then transported by blood (the absorption rate depends on the speciation) prior to deposition in the target organs (e.g. bone, kidney, liver...) in which it is stored and then partially excreted in the urine and faeces. This damage and risk can be mitigated by the use of decorporation agents that reduce internal contamination. Unfortunately, most effective ligands decorporate only a limited range of radionuclides, and some are formulated in ways which are not always very well optimised.

A complete overview and analysis of decorporation studies which have been developed since 2000, shows that the main radionuclides which have been recently studied are uranium, plutonium, thorium, polonium, cobalt, caesium and some metals such as cadmium, lead, aluminium and iron. Concerning ligands synthesised and used for a specific radionuclide either *in vitro* and/or *in vivo*, the main families developed are calixarenes, biphosphonates, siderophores (CAM, hydroxypyridone...), some specific compounds such as dimercaprol (BAL), dithiocarbamates, DTPA and EDTA, penicillamine and trientine, and some natural ligands such as chitosan or pectine.

This review is aimed at presenting: (i) an outline on recent guidance in USA (2006)) and in Europe (2008) on internal radioactive contamination and development of decorporation agents; (ii) a review of the main constraints for radionuclides of interest (U, Pu, Co, Cs, Th, Po, Pb) including some fundamental aspects of their solution chemistry, such as valence states, redox potentials, hydrolysis and complexation properties with proteins (e.g. transferrin); (iii) some new techniques and strategies for synthesizing new powerful ligands such as combinatorial methods, and the development of screening tests to evaluate their efficiency; (iv) the use of *in vitro* test to study the competition between a natural complex formed *in vivo* (e.g. plutonium-transferrin) and a ligand (e.g. DTPA) ; (v) the improvement of a new formulation of DTPA encapsulated in conventional and coated stealth liposomes (100 nm); (vi) and finally the perspectives and future trends with nano-engineered sorbents (e.g. hybrid materials (SiO₂)) or the use of coated magnetic nanoparticles.

Biomimetic Actinide Chelators: Preclinical Development of Orally Active Decorporation Agents

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The threat of a dirty bomb or other major radiological contamination presents a danger of large-scale radiation exposure of the population. Because major components of such contamination are likely to be actinides, actinide decorporation treatments that will reduce radiation exposure became a priority. Current therapies for the treatment of radionuclide contamination are limited and, as outlined by the U.S. Government since the establishment of Project Bioshield in 2003, extensive efforts must be dedicated to the development of orally bioavailable actinide chelators. Our aim is to develop a new therapy for emergency medical use.

Using a biomimetic approach based on the similar biochemical properties of Pu(IV) and Fe(III), siderophore-inspired multidentate hydroxypyridonate ligands have been designed and are unrivaled in terms of actinide-affinity, selectivity and efficiency. A perspective on the preclinical development of two of these actinide decorporation agents will be presented.

The chemical syntheses of both candidate compounds, achieved by coupling the bio-inspired 1,2-HOPO or Me-3,2-HOPO chelating units to polyamine backbones, have been optimized for scale-up. Baseline preparation and analytical methods suitable for manufacturing large amounts under GMP guidelines have been established. Both ligands show much higher actinide-removal efficacy than the currently approved agent, DTPA, with different selectivity for the tested isotopes of Pu, Am, U and Np. No toxicity is observed in cells derived from three different human tissue sources treated *in vitro* up to ligand concentrations of 1 mM, and both ligands were well tolerated in rats when orally administered daily at high doses (> 60 mg/kg/day) over 28 days under GLP guidelines.

Our orally active lead compounds are at least 10 times more effective than DTPA in all efficacy screenings for actinide removal. Preclinical GLP safety toxicology testing in rodents confirms the low-toxicity of hydroxypyridonate-based multidentate ligands. Both ligands are on an accelerated development pathway towards clinical use.

Pharmacological Properties of Orally Available, Amphipathic Polyamino Carboxylic Acid Chelators for Actinide Decorporation

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Commonly used water-soluble polyaminocarboxylic acid (PACA) chelators, such as EDTA and DTPA, require intravenous or subcutaneous administration due to very poor absorption through the GI tract. The bioavailability of PACAs appears to be improved by the addition of side-chains that change their amphipathic properties. Amphipathic triethylenetetramine pentaacetic acid (TT)-based chelators have proven to be efficacious when given orally in experimental studies for decorporation of Pu and Am. To optimize formulations for specific-metal or nuclide chelation, we have compared the pharmacokinetic properties of the chelators relative to differences in lipophilicity. Altering lipophilicity is accomplished by the addition of alkyl side chains of different lengths (from 4-22 carbons) to the TT chelator. ¹⁴C-Labeled C₁₂TT and C₂₂TT chelators are absorbed from the intestinal tract using an *in situ*, gut-loop assay. In the whole animal, the Zn-Na salts of the chelators demonstrate better pharmacokinetic properties than the free acid formulations. Once in the circulation, retention is a function of increasing lipophilic properties. Thus, the longer alkyl chain TT-chelators have a longer retention time in the body than the shorter (less lipophilic) chelators. These amphipathic chelators are excreted by both urinary and biliary routes. Biliary excretion of the amphipathic TT chelators appears to be greater than that reported for DTPA. The addition of a bulky side chain to the TT-based chelators has the potential to interfere with metal binding, first, by removing one carboxyl group and, second, from steric hindrance. However, the chelators exhibit excellent *in vitro* binding affinities for a range of metals, somewhat as expected for PACA-type chelators. Rendering a traditional PACA partially lipophilic by the addition of alkyl side chains may improve pharmacological properties, including oral bioavailability, retention in the body, multiple excretion pathways, and perhaps access to deeper tissue and cellular metal depots. Neutron-induced autoradiography studies clearly demonstrate that the oral administration of the chelators can substantially inhibit the redistribution of ²³⁹Pu in tissues. Ongoing studies are optimizing synthesis and purification methods, establishing the pharmacokinetics with different formulations, and testing these formulations on representative classes of non-radioactive metals as well as different radionuclides. Comparisons are also being made against other chelators such as DTPA.

Functional Sorbents for Selective Decorporation of Plutonium, Uranium, Thorium, and Americium

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Novel decorporation sorbent materials are being developed to protect against radiological terrorist attacks (i.e. dirty bombs). These sorbents, known as the self-assembled monolayers on mesoporous supports (SAMMS™), are a hybrid of organic moieties and ordered mesoporous silica substrate. Batch contact experiments focused on the evaluation and optimization of SAMMS having varying organic head groups for capturing single and multiple radionuclides (Pu, U, Am, and Th) in terms of sorption affinity (K_d), kinetics, pH dependency, selectivity, and stability. An isomer of hydroxypyridinones on mesoporous silica (3,4-HOPO-SAMMS) demonstrated the highest affinity (K_d) for the decorporation of Pu, U, Am, and Th from human blood and plasma; the material also outperformed the FDA-approved actinide ligand diethylenetriaminepentaacetate (DTPA) by a factor of 10^3 -fold. Batch decorporation was extremely fast (complete ~10 min), with optimal performance at pH 6-8, no evidence of protein fouling and less than 0.2% leaching of the Si from the materials. An engineered form of 3,4-HOPO-SAMMS on silica bead (75-200 micron particle size and 60 angstrom pore size) was further evaluated for extracorporeal chelation of radionuclides by externally circulating of human plasma and blood through SAMMS material contained in a microfiltration device. The fluid (~50 mL) was spiked with known concentrations of radionuclide (U, Am, or Pu), gently stirred and pumped (2 mL/min) from a stirred reservoir into the device. The reservoir was sampled every 10 min for two hours to quantify the amount of radionuclide present. Decorporation of U, Am, and Pu from plasma by 3,4-HOPO-SAMMS was rapid and complete with $t_{1/2}$ of 18, 24 and 143 min, respectively. Over 90% of 100 μ g/L of U was removed within 60 min using 3,4-HOPO on silica beads, while only 20% was removed using the best commercially available actinide sorbent, Diphonix resins. This study suggests that SAMMS materials are ideal extracorporeal chelators. Future studies are focused on increasing decorporation efficacy and *in vivo* evaluation in animals. (Supported by NIH/NIAID grant R01 AI0 74064-01)

NIAID/NIH Radiation/Nuclear Medical Countermeasures Development Program

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Exposure to radionuclides disseminated by a radiological dispersion device or deposited as fallout after a nuclear power plant accident or detonation of an improvised nuclear device could result in internal contamination of a significant number of individuals. Internalized radionuclides may cause both acute and chronic radiation injury and increase an individual's risk of developing late health effects such as cancer. The risks of developing health effects can be mitigated by the use of decorporation agents to facilitate the elimination of radionuclides from the body and reduce internal contamination and radiation exposure. Unfortunately, most effective agents decorporate only a limited range of radionuclides, and some are formulated in ways that would make administration in mass casualty situations challenging. There is a need for new radionuclide decorporation agents, reformulations of existing agents, and/or expansion of the label indications for existing treatments. The regulatory pathways for the development and licensure of novel or improved decorporation agents should be understood by researchers and developers so efficient clinical development plans can be developed for these products.

In 2004, the U.S. Department of Health and Human Services directed the National Institute of Allergy and Infectious Diseases (NIAID) to develop a strategic plan and research agenda to guide all National Institutes of Health (NIH) activities contributing to the development of medical countermeasures, including decorporation agents, against radiological and nuclear threats. In 2005, NIAID initiated a research and development contracts and grants program to identify and develop new radionuclide decorporation agents for retention and deployment in the Strategic National Stockpile (SNS). The contracts program identified forms of diethylenetriaminepentaacetate (DTPA) that significantly increase oral bioavailability and demonstrated initial *in vivo* radionuclide decorporation efficacy. Grant programs identified new potential decorporation agents that are orally bioavailable, exhibit low toxicity, and effectively chelate a broader range of radionuclides than currently available drugs in the SNS. Unique radionuclide research facilities at a subcontractor, the Lovelace Respiratory Research Institute, are available to perform decorporation agent screening and pivotal efficacy studies with a broad range of radionuclides to further product development. This poster will highlight the entire NIAID radiation/nuclear medical countermeasures development program, with a particular emphasis on activities related to the development of radionuclide decorporation agents.

Oral Ca- and Zn-DTPA: Efficacy of Oral Formulations to Decorporate Am-241 from Rats after Acute Exposure

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The goal of this project is to test the efficacy of the new oral formulations of Ca- and Zn-DTPA for their ability to decorporate Am-241 from the body after an acute exposure. Currently available only as intravenous products, Ca-DTPA and Zn-DTPA have poor oral bioavailability. Novel oral formulations of Ca-DTPA and Zn-DTPA developed at SRI International (Menlo Park, CA) were administered to rats. Male Fischer 344 rats were administered a single intravenous (iv) tail vein injection of 0.3 μ Ci Am-241 in 150 μ l sodium citrate. The animals were placed in metabolism cages to collect urine and feces for the duration of the experiment. One hour after receiving Am-241, animals were administered an iv (tail vein), oral capsule, or oral tablet dose of Ca-DTPA (at 30 or 60 mg). Each animal received successive doses of Zn-DTPA every 24 h up to 144 h after Am-241 exposure. Urine and feces were collected for 168 h in 24 h fractions. Seven days after the Am-241 dose, the animals were sacrificed, and blood, liver, kidney, femur and remaining carcass were collected. Processed samples of tissues and fluids were analyzed for Am-241 content by liquid scintillation counting and validated against both gamma and alpha spec. Treatment with Ca- and Zn-DTPA significantly increased the amount of Am-241 excreted in both the urine and feces, compared to control groups that did not receive DTPA. In animals receiving DTPA by iv, 78.2 % of the recovered dose was detected in the urine and feces. For animals receiving DTPA orally, 52–72% of the recovered dose was excreted. However, no statistically significant differences between the individual oral DTPA formulations were found in the amounts of Am-241 excreted in the urine and feces. Also, no dose-dependence was observed in excretion rates in animals treated with oral formulations. Treatment with Ca- and Zn-DTPA reduced the Am-241 body burden by 40–69%, depending on dose route.

This work is being supported by NIAID Contract No. HHSN266200500047C.

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Multidentate Hydroxypyridinonate Chelators for the Actinides: Delayed Oral Treatment*

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Octadentate 3,4,3-LI(1,2-HOPO), HOPO (1), is highly effective for *in vivo* chelation of Pu(IV) and Am(III). Tetradentate 5-LIO(Me-3,2-HOPO), HOPO (2), is structurally suitable for chelating Np(V) and U(VI). Treatment is likely to be delayed in human contamination with dispersed radionuclides. Those conditions were approached, using mice, by ligand injection ip at 24h or oral administration at 1 or 24h after an iv actinide injection. Dosages of (1) and (2) were, respectively, 30 and 100 μ molkg⁻¹ ip and 100 and 200 μ molkg⁻¹ oral. Because mixtures of radionuclides may be released, (1) and (2) were combined to take advantage of their differing efficacies for the actinides. Dosages of combined (1) and (2) were, respectively, 30 plus 100 μ molkg⁻¹ injected ip and 100 and 200 μ molkg⁻¹ oral. Actinides in all mouse tissues and excreta were determined using published methods.

Injected at 24h, both HOPOs and their mixture increased Pu(IV) and Am(III) excretion to 5 - 8 times control; appreciable and significant reductions of liver and skeleton actinide were obtained with (1) and the mixture. HOPO (2) and the mixture increased Np(V) and U(VI) excretion to about 3 times control, and significantly reduced liver Np(V) and kidney U(VI) to 30 and 45% control, respectively.

Given orally at 1h, both HOPOs and their mixture increased Pu(IV) and Am(III) excretion to 4 - 7 times control, and significantly reduced both actinides in liver and bone. HOPO (2) and the mixture increased Np(V) and U(VI) excretion to about 115% control, and significantly reduced liver Np(V) and kidney U(VI) to 25 and 50% control, respectively. Oral treatment at 24h with the HOPOs or their mixture increased excretion of Pu(IV) and Am(III) in 24 to 48h to 4 - 8 times control; liver and body actinide were reduced significantly. HOPO (2) and the mixture increased 24 - 48h post-treatment excretion of Np(V) and U(VI) to 2 - 2.5 times control, and significantly reduced liver Np(V) and kidney U(VI) to 50 and 70% control, respectively. In all cases the HOPOs alone or combined increased actinide excretion and reduced tissue actinide more (in most cases significantly more) than similar treatment with CaNa₃-DTPA.

*Work supported by NIAID Project BioShield

MONITORING AND ANALYTICAL METHODS, L. Bertelli, Chair

The Use Of Calix[6]Arene Molecules For Actinides Analysis In Urine: An Alternative To Current Procedures

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Individual monitoring of workers exposed to a risk of internal contamination with actinides is achieved through *in vivo* measurements (anthroporadiometry) and *in vitro* measurements (urine and feces). The procedures currently used for analyzing actinides in urine require lengthy separation associated with long counting times by α spectrometry due to low activity levels. Their main drawback is thus that they are time-consuming, which limits the frequency and flexibility of individual monitoring. In this context, the aim of this work, carried out by the Radiochemistry Laboratory at the Institute for Radiological Protection and Nuclear Safety (IRSN), is to propose alternative radiochemical procedures for the analysis of actinides U, Pu and Am in urine. In order to selectively extract actinides from urines, it is of interest to use calix[n]arene molecules. Indeed, the preorganized structure of these macrocyclic molecules is suitable for the complexation of ions and they can be easily functionalized to be more specific. Thus, the *p*-*tert*butylcalix[6]arenes bearing three carboxylic acid groups or three hydroxamic acid groups are excellent extractants for uranium, and they have also a very good affinity for plutonium and americium. The extraction of actinides by these calixarene has been studied experimentally, and also by computational study for uranium. From these results, a new radiochemical procedure has been proposed for U, Pu, Am analysis in urine. For an application to bioassays laboratories, it was decided to immobilize the calix[6]arene molecules on an inert solid support, for implementation with a chromatographic column. This technique makes it possible to combine the extraction performances of the calix[6]arenes with the practical advantages of the chromatographic column. Consequently, this new radiochemical is well suited for routine analysis. Furthermore, the actinides separation is quantitative and reproducible, and is faster and easier than the current procedures.

Uranium Speciation In Drinking Waters From Drilled Wells In Southern Finland And Its Links To Health Effects

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Exceptionally high concentrations of natural uranium have been found in drinking water originating from drilled wells in Southern Finland. Currently almost 4 % of the Finnish population use bedrock wells as their permanent source of drinking water in rural areas. However, no clear clinical symptoms have been observed among the exposed population. Hence a question arose as to whether uranium speciation in drinking waters could be one reason for the lack of significant adverse health effects regardless of high uranium exposure. Thus the chemical composition of water samples from drilled wells containing up to 3400 $\mu\text{g/L}$ uranium, was analysed. Uranium species were determined using Time-Resolved Laser-induced Fluorescence Spectroscopy. Predictive calculations were carried out using up-to-date thermodynamic data. The results indicated good agreement between measurements and modelling. The low toxicity of Finnish bedrock water may be due to the predominance of two calcium-dependant species, $\text{Ca}_2\text{UO}_2(\text{CO}_3)_3(\text{aq})$ and $\text{CaUO}_2(\text{CO}_3)_3^{2-}$, whose lack of toxicity for cells has been described in earlier studies. This is the first interdisciplinary study describing chemical speciation of drinking water with elevated uranium concentrations and the potential consequence on health. From these results, it appears that modelling could be used to predict the extent of uranium toxicity of drinking water.

Wednesday, May 13, 2009

RADIONUCLIDE BIOKINETICS, F. Paquet, Chair

Determination Of Milk Transfer Coefficients For Four Elements In Four Species Of Grazing Animals

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Models to assess internal radiation doses from environmental releases of radionuclides require radionuclide-specific transfer coefficients to quantitatively estimate the transfer of radioactivity through the food-chain to man. In particular, the transfer of trace elements or radionuclides from pasture grass to milk of grazing animals is important since the quantity of plant material consumed daily, or the area of ground grazed daily by the animals, is extensive and can lead to significant transfer rates. Data from nuclide experiments in which intake rates are kept constant are often summarized as ratios: for radionuclides, Bq/L of milk produced per Bq/d consumed, or for stable elements, $\mu\text{g/L}$ of milk per $\mu\text{g/d}$ consumed (both leading to units of d/L). While data on the transfer of ^{131}I from vegetation to cows' milk have been available for decades, only few data are available on ^{137}Cs , primarily from measurements following the Chernobyl accident. Hence, there is a need for milk transfer coefficient data for other radionuclides and for other animal species that provide fresh milk or dairy products for consumption by man. We conducted experimental measurements on the transfer of stable elements as tracers for radionuclides in four animal species: stable cesium for ^{137}Cs , stable iodine for radioiodine isotopes, and stable strontium for ^{90}Sr in female cattle (i.e., cows), goats (nannies), sheep (ewes) and horses (mares). Breeds were selected to mimic home-owned, non-commercial animals that typically have low-milk production rates. Samples were collected from controlled feeding experiments over 10-days in which the mass of feed consumed daily was controlled. Milk and vegetation samples were collected from four cows, four nannies, four ewes, and eight mares. Milk production was estimated by animal owners either from the size of the animal or from milking a single teat to dryness and measuring the amount of milk collected. The concentrations of stable elements in vegetation and in milk were measured by inductively-coupled plasma mass spectrometry (ICPMS). The transfer coefficient estimates were found to vary by species and by element. Good agreement was found between our iodine transfer measurements and published data on ^{131}I transfer coefficients – suggesting validity of the stable element assessment method. All data and results are summarized in this presentation.

Iodine-131 Biokinetic Study in Ablation Treatment for Thyroid Cancer

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^{131}I has been used in well-differentiated thyroid cancer treatment following subtotal or a near total thyroidectomy. Adequate biokinetic models are required for a realistic assessment of internal dose. This study evaluated the radioiodine biokinetic behavior in the body of ten well-differentiated thyroid cancer adult patients after ^{131}I administration for remnant thyroid tissue elimination purposes. Patients were monitored by *in vivo* and *in vitro* bioassay techniques. Measurements were performed, beginning in the first hour following radioiodine administration. For the *in vivo* measurements in the hospital, a nuclear medicine scintillation probe with a lead filter was used. As the patients left the hospital, the *in vivo* measurements were done at a shielded whole body counting system. Urine samples were collected immediately before the dose administration. All urine voiding were collected and measured on the first 24 hours after radioiodine administration. On the following days, periodically urine samples of the first voiding were collected until measurements reached the minimum limit detection levels - a period of 80 days, approximately. The average values estimated for ^{131}I administered activity fraction eliminated in urine were 67, 90, 94, 95 e 96% at 24, 48, 72, 96 and 120 hours after ablation dose administration, respectively. The maximum value for iodine uptake by remnant thyroid tissue occurred 1 to 5 hours after radionuclide administration. The results suggest that if not all, at least a large fraction of the remnant thyroid tissue is eliminated within eleven to thirteen days after ^{131}I administration for ablation purposes. After this period the retention of ^{131}I in the body may be mathematically represented by the sum of two exponential terms: the first and shorter one with an average biological half-life of approximately 0.81 days (effective half-life = 0.7 days) and the second one, with an average biological half-life of approximately 15 days (effective half-life = 5.2 days). A metabolic model consisting of three initial compartments is proposed, after the 11th -13th days of iodine administration. The cytogenetic dose calculated for those patients, using chromosomal aberration technique, varied from 0.22 to 0.32 Gy.

¹³¹I-Iodide Organ Doses for Hyperthyroid Patients

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The U.S. Public Health Service conducted a study, Thyrotoxicosis Therapy Follow-up Study (TTFUS), of 35,593 patients treated for hyperthyroidism, 23,020 of whom were treated with ¹³¹I, with some patients receiving multiple treatments. This population constitutes the largest group of hyperthyroid patients ever examined in a single study (~90% are Graves' disease patients and ~80% female). A biokinetic model for iodine was developed to derive the dose coefficients for ¹³¹I. The equations relating organ dose coefficients to percent of thyroid uptake were applied to reconstruct organ doses for this cohort. The thyroid doses were calculated taking into account the actual thyroid mass for each patient. The average number of treatments for Graves' patients (male and female) was 1.7 (range: 1 to 29); the average total ¹³¹I administered activity was 370 MBq for female and 407 MBq for male. The average number of treatments for goiter patients (male and female) was 2.1 (range: 1 to 24); the average total ¹³¹I administered activity was 629 MBq for female and 666 MBq for male. The average (\pm SD) dose for female Graves' disease patients were: 0.03 \pm 0.03 Gy for breast, 0.05 \pm 0.04 Gy for red bone marrow, 0.36 \pm 0.49 Gy for urinary bladder (assuming a 3.5-hour voiding interval), 101 \pm 89 Gy for thyroid, 2.1 \pm 2.0 Gy for salivary glands, 1.1 \pm 1.5 Gy for stomach wall, 0.02 \pm 0.02 Gy for colon, 0.04 \pm 0.04 Gy for pancreas, 0.07 \pm 0.06 Gy for lungs, 0.01 \pm 0.01 Gy for ovaries and 0.02 \pm 0.02 Gy for uterus. The average doses for male Graves' disease patients were about 7% higher than the corresponding female average doses, except for breast which is 20% lower. The average doses for goiter patients are 70% higher than those for Graves' patients, except for thyroid, which is only 20% higher.

Natural Accumulation Of Radium-226 In The Human Thyroid Gland And Health Implications

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Small amounts of ²²⁶Ra and other radium isotopes routinely enter the human body through normal dietary intake and in some cases, through occupational exposure. Current radiation dosimetry models for ²²⁶Ra in the human body assume a uniform distribution among soft tissues and a short retention time in those tissues. Those assumptions persist despite publications from the mid-1980s that suggest that radium concentrations in organs should be related to calcium levels, implying that the thyroid gland could accumulate greater concentrations of radium isotopes than any other soft tissue. Moreover, the natural intake or production of sulfate or barium compounds in the body could serve to immobilize the radium in the gland. Evidence of accumulation and immobilization of ²²⁶Ra in thyroids of grazing animals has been documented since the 1960s by one of us (LVM). Little is known, however, about the concentration and retention of radium in the human thyroid. In a collaboration between three institutions, thyroid tissues have been obtained from 105 deceased individuals and measured for ²²⁶Ra content to ascertain concentrations in normal subjects, in five persons involved in uranium mining, and in a single individual who consumed a homeopathic concoction containing ²²⁶Ra. Concentration measurements were made by the sensitive radon emanation technique. Our analysis indicates that the concentrations of ²²⁶Ra in the thyroids from persons from Ohio and Tennessee are 40- to 50-times the reported soft tissue concentrations of 0.003 Bq/kg, the uranium miners were 150-to 800-times reported background concentrations or 5- to 20-times our average concentration. The thyroid tissue concentration in the person who consumed the homeopathic medication was more than 6,000-times the reported background concentration. While the interpretation of these data to thyroid cancer risk is not yet clear, epidemiologic data indicates that thyroid cancers among radium dial painters, among patients who received injections of ²²⁴Ra, and among beagle dogs administered ²²⁶Ra, were all significantly elevated. These findings suggest that the lifetime dose to the thyroid and possibly in other soft tissues, and the related lifetime cancer risks due to natural ²²⁶Ra intakes, may not be fully understood or appreciated.

Quantitative Plutonium Microdistribution In Bone Tissue Of Vertebra From Mayak Worker

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²³⁹Pu is a bone-seeking nuclide, emits an alpha particle, and is a potent carcinogen at sites of its deposition. Epidemiologic studies on cohort personnel of plutonium production indicate a statistical correlation between exposure level from incorporated plutonium and skeleton cancer appearance risk (Koshurnikova et al., 2000). Receiving of quantitative data on Pu microdistribution in different structural elements of human bone tissue will make possible to specify skeleton exposure local dose assessment and to validate dosimetric models. Thoracic vertebra sample was taken for the study from former Mayak worker with rather high Pu burden (44 kBq in body and 20 kBq in skeleton), including information on occupational and exposure history, medical information and data on Pu content in organs. Lexan film autodiagrams were obtained using method of neutron-induced autoradiography from bone tissue sections. Quantitative analysis of randomly selected vision fields on one of autoradiograms was performed: fission fragment tracks Pu in different bone tissue areas were calculated, surface of bone tissue areas were defined. On the basis of obtained data quantitative relation of Pu decays in bone volume to decays on bone surface in cortical and trabecular fractions were defined as 2.0 and 0.4, correspondingly. Actual quantitative relation of decays in bone volume to decays on bone surface is significantly different from recommended by ICRP for cortical fraction. Biokinetic model parameters of extrapulmonary ICRP compartment might need to be adjusted after expansion of data set on quantitative Pu microdistribution in other bone types in human that will involve new cases with different exposure pattern of radionuclide.

Development Of A Physiological Bone Model For Modeling Of Radionuclide And Stable Compounds In Humans

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Abstract – A recently published work indicated that the remodeling portion of the bone surface, rather than the quiescent (endosteal) surface, had the greatest risk of radiation-induced bone cancer, particularly from short-range radiation, due to the elevated dose and the radiosensitizing oxygen effect (Nie and Richardson, *Phys. Med. Biol.* 54, 963 2009). The purpose of this research was to formulate a physiological bone model (PBM) suitable for representing both radioactive and stable elements and compounds that have bone-surface-seeking and bone-volume-seeking characteristics. The PBM is a compartmental biokinetic model that accounts for organic and inorganic processes of bone remodelling in terms of realistic mass transfers, pool sizes, intake and clearance times. An improvement on published models is the allowance for the incorporation of material on different types of bone surface, i.e. quiescent and forming, but also uptake via the canaliculi. Remodelling processes of bone are especially accounted for by formation and mineralization of osteoid and new bone. The PBM is being further developed within the carbon version of the physiological HCNO (hydrogen, carbon, nitrogen, oxygen) model, initially applied to tritium intakes.

Twenty Years of Follow-up for a Hanford Plutonium Wound Case

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A 1985 plutonium puncture wound resulted in the initial deposition of 48 kBq of transuranic alpha activity, primarily ^{239}Pu and ^{241}Am , in the right index finger. Surgical excisions in the week following reduced the long-term residual wound activity to 5.4 kBq, and 164 DTPA chelation therapy administrations over a 17 month period resulted in urinary excretion of about 7 kBq. The case was published in 1988, but now 20 additional years of follow-up data are available. Annual bioassay measurements have included wound counts, skeleton counts, liver counts, lung counts, axillary lymph node counts, and urinalyses for Pu and ^{241}Am . These measurements have shown relatively stable levels of ^{241}Am at the wound site, with gradually increasing amounts of ^{241}Am detected in the skeleton. The liver has generally not shown detectable activity, and lung counts indicate ^{241}Am as shine from the axillary lymph nodes and skeleton. Urine excretion of ^{239}Pu since termination of chelation therapy has typically ranged from 10 to 20 mBq d⁻¹, with ^{241}Am excretion being about 10% of that for ^{239}Pu . In addition, the worker has undergone annual routine medical exams, which have not identified any abnormal conditions associated with the intake.

Twelve Years Of Follow Up Of Cases With Old ^{241}Am Internal Contamination

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Since the early seventies, ^{241}Am has been used for many applications in the Czech Republic, especially for production of AmBe neutron sources and other applications. The original material was AmO₂ powder however the production of some radionuclide sources included chemical treatment of the original material which transformed the americium into the nitrate. The production of sources for smoke detectors was performed by means of powder metallurgy. During these operations, internal contamination of people occurred from time to time.

Workers internally contaminated with ^{241}Am were measured with a whole body counter in early seventies already, however, no special calibration for ^{241}Am was performed and the results of measurement were interpreted very roughly only. No excretion analysis was performed these times. Consequently, when detection technique for in vivo measurement had been improved the people with internal contamination with ^{241}Am were invited in 1997 to join the study including in vivo counting and bioassay measurements. The study started with seven volunteers.

In vivo measurement of the skull activity was performed with 2 LEGe detectors placed near the head of the measured person (since 2008 four detectors). Calibration was performed with skull phantoms of different origin. The main issue related to the calibration was serious difference (about factor of two) among efficiencies obtained from the different skull phantoms. The voxel phantom with Monte Carlo simulation was developed to fit size of heads of individual persons with the aim to decrease uncertainty of activity determination.

Samples of urine and faeces were analysed by means of radiochemical separation followed by alpha-spectrometry. Separation of ^{241}Am from mineralised excreta was performed by combined anion exchange and extraction chromatographic techniques. As a yield monitor ^{243}Am was used.

When the measured data were compared with biokinetic model of americium, it was found that in most cases after more than 15 years since the intake, the excretion rate is lower (or skeleton activity higher) than predicted. On the other hand the ratio of excreted activity in urine and faeces given by model is in accordance with the measurements. An effort was made to vary model parameters to reach a better fit with the experimental data

This programme was supported by the project of the State Office of Nuclear Safety of the Czech Republic 3/2006.

Thursday, May 14, 2009

DOSE ASSESSMENT, D.R. Fisher, Chair

Dose Coefficients Of ^{141}Ce , ^{144}Ce , ^{95}Zr And ^{90}Sr Using Voxel Phantom Safs For Photons And Electrons

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The radionuclides ^{141}Ce , ^{144}Ce , ^{95}Zr and ^{90}Sr are products of nuclear testing, uranium and plutonium fissions and nuclear weapons. These radionuclides undergo beta decay accompanied with photon emission from the newly formed daughter nucleus. Current dose coefficients were derived using mathematical representations of the body (so-called phantoms) developed at the Oak Ridge National Laboratory (ORNL). In these calculations, the beta emissions only irradiate the organ within which the radionuclide resides and for walled organs a fixed fraction of the emitted energy is absorbed within the wall. For the active marrow and bone surface targets absorbed fractions were explicitly provided in ICRP Publication 30. ICRP Publication 66 and 100 contain further detailed energy dependent absorbed fraction data for the airways and the segments of the alimentary tract. In contrast to mathematical phantoms, voxel phantoms for reference male and female recently developed at the Helmholtz Zentrum München – German Research Center for Environmental Health (HMGU) in collaboration with the Task Group DOCAL of ICRP Committee 2 were constructed from computed tomographic (CT) scans of individuals. These voxel phantoms are more realistic in shape and location of organs in the body; therefore they are providing photon and electron SAFs for solid organs that are more precise than those from mathematical phantoms. However, for the skeleton the small target regions of interest cannot be represented in the voxel phantoms due to limited spatial resolutions and has been developed based on micro CT as undertaken at the University of Florida. The voxel phantom SAFs derived for photons and – as far as applicable – electrons are integrated into the code SEECAL developed at ORNL. The dose coefficients for these beta emitters are calculated and compared with the current values in ICRP publications. Changes in organ doses between these two sets of dose coefficients are discussed.

Dose Conversion Factors For Radon – How Should They Be Calculated?

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Radon, ^{222}Rn , is a naturally occurring radioactive gas, with a half life of 3.8 days, formed as the decay product of radium-226 in the uranium series. Radon gas emanates from the earth's crust and as a consequence is present in the air outdoors and in all buildings, including workplaces. Radon decays to isotopes of solid elements (^{218}Po , ^{214}Pb , ^{214}Bi), which if inhaled results in relatively high doses to the lung.

Radon has long been recognised as a cause of lung cancer and it was identified as a human lung carcinogen in 1986 by the World Health Organisation. The main source of information on risks of radon induced lung cancer has been epidemiological studies of underground miners and more recent studies have provided informative data on risks at lower levels of exposure. The information now available on risks of residential and occupational exposure to radon is sufficient for control to be based on levels of exposure rather than estimates of dose. However, dose estimates are of value for protection purposes when workers are exposed to more than one source of radiation and they also allow comparisons to be made of sources of public exposure.

Effective doses from radon have been calculated in two ways: the so-called “epidemiological” and “dosimetric” approaches. The ICRP (1993) recommended an epidemiological approach in which the risk of lung cancer per unit radon exposure (in Working Level Months; WLM) was compared with the total detriment per unit effective dose (in sieverts, Sv). The former is determined from miner epidemiology and the latter determined mainly from Japanese atomic bomb survivor epidemiology. Hence, values of mSv (effective dose) per WLM were obtained and referred to as the dose conversion convention. Alternatively, various dosimetric models of the human respiratory tract, including the ICRP (1994) model can be used to estimate equivalent dose to the lungs and effective dose per unit exposure to radon progeny. As a result of these two methods different organisations, notably by ICRP (1993) and UNSCEAR (2000) used or recommended different dose conversion factors.

An ICRP task group, headed by Margot Tirmarche, was asked to review recent epidemiological studies and recent dosimetric calculations in order to recommend an appropriate value for the effective dose per unit exposure to radon progeny for radiation protection purposes. Based upon the work of this task group, proposals for revisions to the calculation of doses from radon progeny are discussed in this paper. Both the “epidemiological” and “dosimetric” approaches are revisited in the light of new data and compared. The implications of the estimated dose values for reference values are also discussed.

Consideration Of Uncertainties In The Monitoring Of Internal Contamination

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Potential internal contaminations of workers are monitored by periodic bioassay measurement interpreted in terms of intake and committed effective dose through biokinetic and dosimetric models. After a prospective evaluation of exposure at a workplace, a suitable monitoring program can be defined by the choice of measurement techniques and frequency of measurement. However, the actual conditions of exposure are usually not well defined and the measurements are subject to errors.

In this study we considered the uncertainties associated with a routine monitoring program in order to evaluate the minimum intake and dose detectable for a given level of confidence. Major sources of uncertainties are the contamination time, the size distribution and pulmonary absorption of the incorporated particles, and the measurement errors. Different assumptions may be applied to model uncertain knowledge which lead to different statistical approaches. The available information is modeled here by frequentist or Bayesian probability distributions that are aggregated by stochastic or fuzzy arithmetic. These methods are implemented in the OPSCI software under development.

This methodology was applied to the monitoring program of plutonium workers at the AREVA NC reprocessing facility (La Hague, France). The uncertainty study showed that the current program can detect annual intake leading to committed effective dose of 1 mSv for a confidence level of 95 %.

Our methods may be used for assessment of any other monitoring program, through the criteria of uncertainty on estimated dose and minimum detectable intake for a given confidence level. Furthermore they allow an optimization of the program, as a compromise between the corresponding minimum detectable dose, compared to a set dose constraint, and the cost of the monitoring.

Modelling Intersubject Variability Of Bronchial Doses For Inhaled Radon Progeny

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In radiation protection, bronchial doses are routinely calculated for a standard or reference man by assuming defined average values for all anatomical and physiological parameters involved in radon lung dosimetry, therefore providing a single dose value for specified exposure conditions. In reality, however, these anatomical and physiological parameters may vary significantly among different subjects, hence producing a range of bronchial doses for the same exposure conditions.

The main sources of intersubject variations considered in the present study were: (i) size and structure of nasal passages, affecting extrathoracic deposition and, in further consequence, the fraction of the inhaled activity reaching the bronchial region, (ii) volume and branching asymmetry of the human bronchial airway system, leading to variations of diameters, lengths, branching angles, etc., (iii) respiratory parameters, such as tidal volume, breathing frequency and inhalation/exhalation times, (iv) mucociliary clearance velocities and slow bronchial clearance fraction, and, (v) thickness of the bronchial epithelium and relative fractions of target cells.

For the calculation of deposition fractions, retained surface activities and bronchial doses, anatomical and physiological parameter values were randomly selected from their corresponding probability density functions, derived from experimental data, by applying Monte Carlo methods. Bronchial doses were computed for specific home and mining conditions, i.e. for defined size distributions, unattached fractions and physical activities. Resulting bronchial dose distributions could be approximated by lognormal distributions with median values of 7.7 mGy/WLM for homes and 7.9 mGy/WLM for mines, yielding a K-factor of about 1. Geometric standard deviations (GSD), illustrating intersubject variations, ranged from about 2.5 in large bronchi to about 8 in peripheral bronchiolar airways. While intersubject variations in central bronchial airways were caused primarily by the attached fraction, the variability in the peripheral bronchiolar region was dominated by the unattached fraction. Differences in exposure conditions between homes and mines hardly affected the degree of dose variability.

In conclusion, the major sources of the intersubject variability of bronchial doses for inhaled radon progeny are the asymmetry and variability of the linear airway dimensions, the filtering efficiency of the nasal passages and the thickness of the bronchial epithelium, while fluctuations of the respiratory parameters and mucociliary clearance rates seem to compensate each other.

Uncertainties In Internal Dose Assessment

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Abstract. NCRP Scientific Committee 6-3 has nearly completed the preparation of a report in which the current state of knowledge of uncertainties in internal dose assessments is extensively reviewed. The types of uncertainty that are associated with internal exposures that occur in the occupational, environmental, and medical fields, may result from intravenous administration or from intakes by inhalation, ingestion, or absorption through intact or damaged skin, may address past exposures that are based on measurements or future exposures that are based on models, and may be related to specific individuals, for whom some anatomic or physiological parameter values may be known, or to unspecified individuals, for whom group values must be assumed, are discussed in the report. The uncertainties in the measurements, in the activity intakes, in the dosimetric model structure and in the model parameters, are covered in separate section of the report. For a number of important elements, the uncertainties in the doses per unit intake are estimated for a range of defined conditions.

A large part of the report is devoted to the presentation of examples of situations in the occupational, environmental, and medical settings in which the quantification of the uncertainties in internal dose estimates is warranted or desirable. The examples illustrate the use of the statistical techniques described in the report. They are ranked in order of increasing difficulty, from the simplest one, in which the uncertainty is determined arbitrarily as a policy decision, to the most complex example, which requires the use of an extensive Bayesian analysis. Although detailed technical information cannot be provided at this stage, the main issues discussed in each section of the report will be presented.

Three Plutonium Chelation Cases at Los Alamos National Laboratory

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In three recent cases of wounds contaminated with ²³⁹Pu, chelation with DTPA was undertaken. All cases were finger punctures, and each chelation injection contained the same dosage of DTPA. One subject was chelated only once, while the other two received multiple injections. One case was particularly well documented with additional measurements of wound, urine, and excised tissues. These additional measurements served to improve the estimate of the efficacy of the chelation treatment.

The efficacy of the chelation treatments is compared for the three cases. Results are interpreted using chelation models, and useful heuristics for estimating the intake amount and final committed dose are presented

Case Study: Three Acute ²⁴¹Am Inhalations with DTPA Therapy

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Three workers incurred inhalation exposures to ²⁴¹Am oxide as a result of waste handling and compaction. The magnitudes of the exposures were not fully recognized until the following day when an in vivo chest count identified a significant lung deposition of ²⁴¹Am in a male worker, and DTPA chelation therapy was initiated. Two additional workers (one female and one male) were then identified as sufficiently exposed to also warrant therapy. In vivo bioassay measurements were performed over the ensuing six months to quantify the ²⁴¹Am activity in the lungs, liver, and skeleton. Urine and fecal samples were collected and showed readily detectable ²⁴¹Am during this period. Clinical lab tests and medical evaluations all showed normal results. There were no significant adverse clinical health effects from the therapy. The estimated ²⁴¹Am inhalation intakes for the three workers were 1800 Bq (48 nCi), 630 Bq (17 nCi), and 150 Bq (4 nCi). The three underwent slightly different therapy regimes, with the final assessed doses relative to the potential doses without therapy being 22%, 52%, and 60%, respectively

Biokinetic Modeling Of DTPA Decorporation Therapy: The CONRAD Approach

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Diethylene Triamine Pentaacetic Acid (DTPA) is used for decorporation of plutonium (Pu), because it is known to be able to enhance urinary excretion for several days after treatment by forming stable Pu-DTPA complexes. The decorporation of Pu prevents accumulation in organs and results in a dosimetric benefit, which is difficult to quantify from bioassay data using existing models. The development of a biokinetic model describing the mechanisms of actinide decorporation by administration of DTPA was initiated as a task in the European COordinated Network on RADIation Dosimetry (CONRAD.) The systemic biokinetic model from Leggett et al. (published in 2005) and the biokinetic model for DTPA compounds of ICRP Publication 53 were the starting points. A new model for biokinetics of administered DTPA based on physiological interpretation of ¹⁴C-labelled DTPA studies from literature was proposed by the group. Plutonium and DTPA biokinetics were modelled separately. The systems were connected through the chelation-process of Pu atoms and DTPA molecules to Pu-DTPA complexes which was described as a 2nd order kinetics. It was assumed that chelation only occurs in the blood and in compartment ST0 (representing rapid turnover soft tissues), and that Pu-DTPA complexes and administered forms of DTPA share the same biokinetic behaviour. First applications of the CONRAD approach showed that the enhancement of Pu urinary excretion after administration of DTPA was strongly influenced by the chelation rate constant. Setting it to a high value resulted in a good fit of observed data. However the model was not yet satisfactory since the effects of repeated DTPA administration in a short time period can not be predicted in a realistic way. In order to introduce more physiological knowledge to the model several questions still have to be answered, notably

- Where are the Pu-DTPA complexes formed?
- Which biological ligands of Pu are dissociated?
- Is the in-vivo stability of the Pu-DTPA complexes depending on the environment?
- Is the biokinetics of Pu-DTPA excretion similar to that of DTPA?

Further detailed studies of human contamination cases and experimental data will be needed in order to address these issues. The work is now continued within the European Radiation Dosimetry Group EURADOS.

Posters

Modeling Deterministic Effects In Hematopoietic System Caused By Chronic Exposure To Ionizing Radiation In Large Human Cohorts

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A new model of the hematopoietic system for humans chronically exposed to ionizing radiation (IR) allows for quantitative description of the initial hematopoiesis inhibition and subsequent recovery with taking into account individual specifics of an organism at reducing dose rate. An advantage of the model is the possibility for quantitative estimation of the relationship between peculiarities of the short-term response patterns in hematopoietic system and probabilities of long-term effects (e.g., leukemia, chronic cytopenia).

This model takes into account the dynamics of the hematopoietic stem cell (HSC) compartment as well as the dynamics of each of the three blood cell types (leukocytes, erythrocytes, and platelets). Short-term dynamics is described by the system of delay-differential equations and long-term dynamics is described by a steady-state solution. For a specific blood line (e.g., lymphocytes) the model includes nine parameters which are initially estimated from the results of other experiments. They include a) an initial steady-state of peripheral lymphocytes for an unexposed organism and its ratio to an initial steady-state of the numbers of HSC; b) an amplification number, c) a parameter describing the proliferation/apoptosis balance in HSC; d) apoptosis of peripheral lymphocytes; e) scale parameters of feedback functions; and f) characteristics of radiosensitivity (D_0 's) of HSC and peripheral lymphocytes. The dynamic model of hematopoiesis is applied to the data on subcohort of the Techa River residents with longitudinal hematological measurements (e.g., blood counts) performed in 1951-1956 to 1970 (which totals in about 10,000 exposed individuals). Among well described effects observed in these data are a) the slope value of the dose-effect curves describing the hematopoietic inhibition due to chronic IR and b) the dose rate patterns of the fractions of cytopenic states (e.g., leukopenia, thrombocytopenia).

The developed model of hematopoiesis can be used as a unique tool for prognosis of individual risks of the development of radiobiologic effects in the hematopoietic system in short- and long-term time period after the onset of exposure. The prognoses can be used in the elaboration of approaches to preventive arrangements in situations of emergencies with exposure of large population groups.

Whole-Body Measurements Of Workers Occupationally Exposed To Radionuclides At IPEN, - Brazil

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The intake of radioactive material by workers can occur in the radiopharmaceuticals production, during the handling of these in the medical fields (nuclear medicine) and in biological and research laboratories. The workers who work in areas where exposures are significant are routinely monitored to demonstrate that the workers are receiving adequate protection from internal contamination. Direct measurements of whole-body and thyroid contents provide an estimate of the activity of these radionuclides in the potentially exposed workers. The whole-body measurements of the workers, trainees and visitors are routinely performed by the In Vivo Monitoring Laboratory (LMIV) of the Energy and Nuclear Research Institute (IPEN/CNEN-SP). The frequency of measurements is defined by the Radioprotection Service (SRP) and the Dose Calculation Group of IPEN. During the period January 2007 to December 2008, 2600 measurements had been carried in workers who develop tasks related to the production and research. The activities of the radionuclides and the workers' tasks relationship had been evaluated.

Testing of Individual Sensitivity to Radon and Thoron Exposure by *In Vitro* Irradiation of Lymphocytes Culture

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The shape of the dose-response relationship for cancer risk at low doses and/or low dose rates for adverse health effects is a critical issue for radiation protection policy according with UNSCEAR 2000; CERRIE 2004; French Academy 2005; NRC 2006; ICRP 2007. Differences in radiation sensitivity between individuals, or groups, raise the ethical and policy question as to whether some individuals, or groups, are inadequately protected by the present system and regulations. Therefore, research is needed to identify the factors that affect individual sensitivity to radiation risk and to obtain realistic estimates of how large the differences may be in extreme cases and also the spread of sensitivities in average population groups. DNA damage response processes are likely to play an important role in radiation-associated cancer risk. So, this paper tries to quantify the individual sensitivity using comet assay test. Scoring of induced lesions at DNA level was quantify for lymphocytes culture exposed *in vitro* to the same doses of Radon and Thoron emitted by pitchblende ore. The study was done for healthy donors, comparatively with disease donors. Ageing *in vitro* of lymphocytes culture exposed to low doses of ionizing radiation is the biological model used, which are presented here.

Optimization of ^{99m}MO Measurement in ^{99m}Tc Eluate Samples Using a Scintillation Detection System

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Molybdenum-99 is the parent of ^{99m}Tc, a radionuclide widely used in nuclear medicine for image diagnose. During elution of ^{99m}Mo/^{99m}Tc generators ^{99m}Mo might be extracted depending on the quality and integrity of the generator and handling conditions at the radiopharmacy laboratory. One of the parameters used to state the quality of ^{99m}Tc eluates is the radionuclidic purity, MBT (molybdenum breakthrough), defined as the ratio between ⁹⁹Mo and ^{99m}Tc activities in eluates. The maximum ⁹⁹Mo concentration established by European Pharmacopoeia is 0.1%. The International Atomic Energy Agency (IAEA) suggests a limit of 0.015%. ⁹⁹Mo emits high-energy beta particles and its presence as a radionuclidic impurity in the eluate increases unnecessarily the dose to the patient. Furthermore, depending on its activity in the radiopharmaceutical solution, and considering its gamma emission of 740keV and affinity to the liver, it can also degrades the quality of the diagnose image. The objective of this work is to develop a methodology to identify and quantify ⁹⁹Mo activity in ^{99m}Tc eluates. A NaI(Tl)8x4 scintillation detector installed in the shielded room of the IRD whole body counter was calibrated by determining three efficiency curves using a standard solution containing ¹³⁹Ce, ¹³⁷Cs, ⁸⁸Y and ⁶⁵Zn. The solution was transferred to a glass vial and positioned in 3 distances (10, 15 and 20cm) from the detector face and the vial support. The methodology was validated by measuring a standard solution containing a known activity of ⁹⁹Mo. This methodology was applied to measure a series of ^{99m}Tc eluate samples collected in nuclear medicine centers located in the city of Rio de Janeiro. All measurements indicated the presence of ⁹⁹Mo. It was concluded that the technique is sensitive to detect ⁹⁹Mo in ^{99m}Tc eluates at levels below international limits suggested by IAEA for radionuclidic impurity.

Evaluation Of The Internal Exposure In A ^{123}I Production Plant Through In Vivo Monitoring

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^{123}I is a photon emitter radionuclide (159 keV) used in nuclear medicine for image diagnosis of a variety of diseases. It has been produced at the Institute for Nuclear Energy (IEN) since 1998 and supplied to nuclear medicine centres located in the State of Rio de Janeiro. The IEN has increased its production in about 500% in the first five years in order to respond to the increasing demand from the clinics for Meta-iodine-benzyl-guanidine (MIBG). The production of the radiopharmaceutical MIBG as well as the annual maintenance of the cyclotron can lead to internal exposures of the workers by ^{123}I and ^{65}Zn . Such workers have been monitored routinely at the IRD Whole Body Counter. Monitoring is based on in vivo measurements of the thyroid and whole body for the determination of ^{123}I and ^{65}Zn respectively. This work presents the techniques performed at the IRD whole body counter for the identification and quantification of ^{123}I and ^{65}Zn . It is also discussed the methodology adopted for data interpretation in terms of committed effective doses as well as an evaluation of the results of the in vivo measurements. It is concluded that (i) the measurement techniques are suitable for routine monitoring of occupationally exposed workers and (ii) the radiopharmaceutical production plant is safe in terms of radiation protection conditions since all incorporations detected so far represent only a small fraction of the annual dose limits.

A Mobile Bioassay Laboratory for the Assessment of Internal Doses, Based on In Vivo and In Vitro Measurements

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Accidental internal exposures may occur in practices such as nuclear power reactor operation, production of radioisotopes and use of unsealed radioactive sources in medicine and research. Such practices require an infrastructure for quick response in the case of nuclear and radiological accidents of a wide range of magnitudes. The goal of this work is to design and calibrate a mobile laboratory for the mitigation of accidents involving workers and population exposure as well as for routine monitoring of internal contamination. The detectors available in the mobile laboratory can identify and quantify photon emitters in the energy range of 100-3000 keV in the whole body, organs or tissues and in urine samples. The system was set up in a truck with internal dimensions of 3.30m x 1.60m x 1.70m. A thyroid monitor consisting of a lead-collimated NaI(Tl) 3"x3" was calibrated with a neck-thyroid phantom developed at the IRD. Whole body measurements are performed with a NaI(Tl) 8"x4" calibrated with a plastic-bottle phantom containing solutions of radionuclides uniformly distributed among its various sections. A portable body counter assembled on a tripod is also available in the mobile lab. Urine samples are measured with another NaI(Tl) 3"x3" detector set up in a steel support. Standard radionuclide solutions were prepared and certified by the National Laboratory for Metrology of Ionizing Radiation (LNMRI) located at the IRD. In vitro measurements of urine samples use a calibration curve of efficiency versus energy for standard volumes. In vivo and in vitro detection limits were converted to minimum committed effective doses for the radionuclides of interest using current biokinetic and dosimetric models to evaluate the applicability and limitations of the system. Dose detection limits obtained for the activation and fission products of high energy show that the system sensitivity is suitable for use in emergency situations as well as in routine monitoring of workers subject to risk of internal exposure by such radionuclides.

Biological Responses To Internal ¹³⁷Cs: A Model For A RDD.

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Our group is currently involved in examining the normal tissue late effects that may be observed in the lung from radiation exposure following a radiological dispersion device (RDD). One component of the risk of exposure will come from the fact that exposure can occur internally. Cesium has been identified as a likely component of such a device due to its widespread use and, we therefore have begun to develop a murine model for internal contamination, using soluble cesium particles. In the initial studies, we investigated the effects of administration of two single doses of cesium, 10 μCi and 50 μCi , in groups of 5 C57BL/6 female mice. Blood and serum was sampled at the time of sacrifice to look at cell counts and release of cytokines and identification of markers of response using an unbiased proteomics approach. In addition, lung and other acutely responding tissues (e.g. colon) were taken for histology and protein and mRNA analysis. Our results indicate that these relatively low single doses of internal cesium had effects, as measured by cell differential counts, and also induced an immediate inflammatory response in the lungs, as measured by neutrophil and macrophage analyses. At 28 serum protein profiles identified a number of significant alterations that may prove useful in assessing radiation injury. However, elimination of the radioactive cesium appeared to be faster than would have been predicted by ICRP 30. Studies therefore are underway to examine internal contamination at different dose levels, looking in particular at tissue dispersion and response. This work was supported by NIAID U19 AI-067733.

Intracellular Decorporation of Pu/Am by Different Galenic Forms of Ca-DTPA

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Intracellular penetration of free DTPA is considered to be negligible so that Pu/Am decorporation might mainly involve extracellular monoatomic actinides in circulating fluids. Injection of DTPA encapsulated within liposomes, or pulmonary administration of DTPA aerosols have been proposed to improve liver and lung decorporation, respectively. This study compares, in the rat, intracellular decorporation by 3 galenic forms of Ca-DTPA. When Ca-DTPA solution is administered i.v., 1h after actinide-citrate i.v., most urinary decorporation occurs within a few hours (extracellular decorporation), but delayed excretion is observed later on, corresponding to 5-10% of the decorporated actinides. DTPA efficacy depends on its dose and negligible extracellular decorporation is expected for Pu at doses less than $1\mu\text{mol.kg}^{-1}$. When Ca-DTPA is administered 24h before contamination, DTPA in blood is then 0.025% of the initial dose and equilibrium of remaining DTPA with other cations (Fe, Zn...) is achieved. After pre-treatments at 30 and $300\mu\text{mol.kg}^{-1}$, Pu urinary excretion fits to single exponential functions of time ($T_{1/2}\sim 3\text{d}$). Moreover, at $300\mu\text{mol.kg}^{-1}$, a nearly total liver decorporation is observed (hepatic DTPA/Pu ratio $\sim 2.10^3$). Specific liver contamination is obtained after i.v. of Pu-phytate solution. A 90% liver decorporation is observed for liposomes at $3\mu\text{mol.kg}^{-1}$ (hepatic DTPA/Pu ratio $\sim 1.10^3$), whereas, a similar decorporation, 40%, is obtained for liposomes ($0.03\mu\text{mol.kg}^{-1}$) and solution ($30\mu\text{mol.kg}^{-1}$). For each treatment, exponential decrease of Pu urinary excretion is observed ($T_{1/2}\sim 6\text{d}$). Pulmonary contaminations are obtained after intratracheal injection of ²³⁸⁻²³⁹Pu-nitrate ($\sim 10\%$ colloids) or inhalation of PuO₂ containing 47% Am (alpha activity). In this latest case, $\sim 90\%$ of dissolved actinides correspond to Am. Single (+2h) or repeated treatments (+2h, 1, 2, 3, 4d) are performed by i.v. of solution ($30\mu\text{mol.kg}^{-1}$) or pulmonary insufflation of dry powder ($20\mu\text{mol.kg}^{-1}$). For Pu-nitrate, efficacy of pulmonary decorporation gradually increases from 1 i.v. (15%) to 1 insufflation, 5 i.v. and 5 insufflations (80%). After the first insufflation, DTPA/Pu ratio is estimated at 2.10^3 . By contrast, for PuO₂, similar decorporation of dissolved actinides ($\sim 90\%$) is observed whatever the treatment schedule and, for insufflation, the pulmonary DTPA/dissolved-actinide ratio is $\sim 5.10^8$. Altogether, these results shows that intracellular decorporation of Pu/Am can be obtained by various galenic forms of DTPA, and similar decorporation efficacy is observed within different intra or extracellular retention compartments, depending on specific free-DTPA/actinide ratio.

Effects Of Incorporated Radionuclides On Hydrobionts Within The Chernobyl Accident Exclusion Zone

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Our researches were carried out during 1999-2008 in Azbuchin Lake, Yanovsky Crawl, Dalekoye-1 Lake, Glubokoye Lake, Uzh River and Pripjat River within the Chernobyl accident exclusion zone. The chromosome aberration rate in embryo tissue of gastropod snails and in root meristem of higher aquatic plants was studied. The results compared to the data received for hydrobionts from control lakes, located within the Kiev City area. The absorbed dose rate registered in range from 1.3 mGy/year to 3.4 Gy/year. The highest rate was found in Dalekoye and Glubokoye lakes, the lowest - in the Pripjat River and Uzh River. Hydrobionts from the control lakes were characterized by absorbed dose rate about 0.3 mGy/year. The rate of chromosome aberration for snails from the control lakes was about 1.1-2.0%. About 3.3 and 5.7% of aberrant cells was registered in snail's embryo from the Pripjat and Uzh rivers respectively. The highest rate of aberration was found in snails from lakes within the dammed territory on the left-bank flood lands of the Pripjat River (Dalekoye-1 and Glubokoye lakes) - 21-23%. In the embryo tissue of snails from Yanovsky Crawl chromosome aberration rate was about 18% and in Azbuchin Lake - about 20%. The highest chromosome aberrations rate in root meristems (17.8-10.8%) were registered in plants from lakes within the left-bank flood lands of the Pripjat River, the lowest one (4.5-2.2%) - in plants from the Pripjat and Uzh rivers. The positive correlation between chromosome aberration rate and absorbed dose rate from incorporated radionuclides was determined. In hemolymph of snails from Dalekoye-1, Azbuchin and Glubokoye lakes the quantity of death cells averages 36.2%, 39.2% and 43.8% respectively, the part of phagocytic cells averages 44.3%, 41.2% and 45.0%, as well as decrease of the young amoebocytes quantity to 13.2%, 20.1% and 9.5% respectively. The insignificant quantity of abnormal cells and micronuclei has been observed as well. In the control water bodies the part of death cells averages from 2.2 to 5.3% and the quantity of phagocytic was at level 3.0-4.2%. The quantity of young amoebocytes has increased here to 79.7-89.6%.

Dissolution Of Thorium And Uranium From A Therapeutic Soil In A Synthetic Gastrointestinal Fluid

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Abstract:

The aim of this study is to assess the bioaccessibility of thorium and uranium from soil, which provides an estimate of the fraction of contaminant in soil potentially available for absorption. The healing soil, finding application in humans for medical reasons such as acid reflux, consisted of 10.4 ppm thorium and 4.9 ppm uranium, respectively. The fractional dissolution of thorium and of uranium from soil was determined in synthetic gastric and intestinal fluids using an in vitro method simulating digestion conditions after the oral intake of the healing soil. Soil samples were first incubated in gastric juice for 2 hours at 37°C. The gastric solution comprised mainly of hydrochloride and pepsin (pH 1.5-2). Then, the incubation continued with added intestinal fluid (pH 7.5) for further 2 or 6 hours, respectively. Two different intestinal juices were used: 1) sodium bicarbonate solution, taken from the in vitro US Pharmacopoeia digestion method, and 2) solution with organic compounds (enzymes), the latter method adopted from an in vitro digestion model from Germany (DIN 19738). After the end of incubation, the incubation solutions were centrifuged and filtered. The concentration of thorium and uranium in the filtrates dissolved from the soil were measured using inductively coupled plasma mass spectrometry. Thorium and uranium solubility from soil was 0.5 to 8%, and 0.2 to 5%, respectively, depending on the soil to solution ratio, and the method used. Incubation of soil in the intestinal fluid and the following pH rise obtained a 4-6 times reduction of solubility for thorium possibly indicating a precipitation of Th or rebinding of Th to soil. Addition of intestinal juice together with pH increase showed no conclusive result of uranium dissolution from soil; however, an enhanced solubility of uranium is indicated. In general, bioaccessibility of thorium and uranium from the therapeutic soil in the gastrointestinal tract is small and the application for medical reason should not be of concern to human health.

Calculation and Assigning of Internal Doses from Derived Air Concentration (DAC) of Radioactive Aerosols with Natural Uranium in Nuclear Fuel Plant -Pitesti

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Occupationally workers dealing with bulk quantities of material with enhanced activities of natural uranium are exposed to external radiation. Furthermore inhalation of uranium dust may occur. The paper present a rapid system for evaluation the internal doses of NFP occupationally workers.

In NFP three types of solubility classes for natural uranium are presented F(M), M.

The main work places where the high concentration of radioactive aerosols are occurred are monitored with Aerosols Sampling Central System (ASCS). Than, the samples are gathered and measured for alpha activity with automatic counter TENNELEC LB-5100 and the Derived Air Concentration (DAC) are calculated. Based on ICRP-68 coefficients for an AMAD of 5 μm , the internal doses for workers that working in these places are calculated. During few years the evaluation of internal doses is done and the conclusions of the average level of these doses for different solubility classes of natural uranium are resulting. No chemical toxicity, no worn. of protective respirators, no elimination of uranium by urine and faeces or spending the time in those places are taken in account.

By adding of external doses measured with film badge we obtain the estimated annually effective dose. The assessment give us means to restrict the activity in some work places. A simple software for internal doses is prepared for quickly evaluation.

Applications of the Laser Spectroscopy for Actinides Trace Amount Detection and Valence States Determination

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Determination of valence states of various elements, including Pu and U, occurring in various biological subjects in trace amounts, is extremely important problem in biology and medicine, since the behavior of trace amounts of elements essentially depends on their valence states. In particular, the valence states of radionuclides govern to a large extent the transport and metabolic processes responsible for accumulation of radionuclides and their removal from organs and tissues. The most urgent problem is determination of valence and chemical forms of occurrence of such actinides as Pu and U in various biological subjects.

Data on valence states of actinides in biological subjects allow conclusion on the features of actinide distribution in biological subjects and elucidation of the features of reactions of actinides with biological media. The α -spectroscopy and traditional resonance ionization spectroscopy (RIS, RIMS) allow detection of actinide elements in biological samples with high sensitivity but do not allow determination of their valence states [1]. At present the most efficient methods of detection of actinides and lanthanides in solutions are methods based on registration of actinides with time resolution, time-resolved laser induced fluorescence (TRLIF) spectroscopy, having [1] limit of detection (LOD) up to 10-13M (mol/l), 1 ml of a solution is required for analysis.

Unfortunately, Pu, Np, and also a number of valence forms of uranium give no direct luminescence in solutions. For determination of valence forms of Pu, Np, and a number of valence forms of U not most sensitive methods of laser spectroscopy are used [1]. Among them are laser induced photoacoustic spectroscopy (LIPAS) with LOD 10-7M, absorption spectroscopy with LOD 10-5M, and laser spectroscopy with the use of effects of thermal lens (TLS) with LOD 10-6 M.

We observed experimentally the chemiluminescence of solutions induced by complexes containing excited actinides (Pu, Np, and U) [1, 2] and demonstrated a possibility of using chemiluminescence method for detection and determination of valence states of Pu, Np, and U with high sensitivity.

The main subject of this report is discussion of the possibility of laser spectroscopy and chemiluminescence using for detection of trace amounts of actinides (with LOD up to 10-11M, 1ml of a solution is required for analysis) in biological samples with parallel determination of valence states of actinides and application of this procedure to detection of actinides in biology and medicine.

This work was supported by International Science and Technology Centre (ISTC), project ISTC 3694.

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Study On The Administration Strategy Of The Potassium Iodide (KI) In A Nuclear Emergency

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Abstract: In a breach-of-containment nuclear accident, the near-field exposure is primarily through of radioiodine. Thyroid blockade by oral potassium iodide (KI) is a practical and effective measure for the general public in such an emergency. Administration of KI at the appropriate times can block most of the thyroidal uptake of radioiodine. Therefore, the assessment of thyroid dose by inhaled radioiodine should take into account the associated effect of thyroid blocking. In the previous research, the retention functions incorporating the thyroid blocking effects by KI were derived to calculate the blocking factor, and thyroid doses were then evaluated by accounting the effects of thyroid blockade. The efficacy of the blockade and the risks of thyroid side effects depend on individual and external factors. The benefits also depend on age. Therefore administration strategy of KI according to age is necessary and this strategy should be addressed in emergency plans for the case of repeated KI doses. In this study, the administration strategy of KI in a nuclear emergency (such as dose, administration interval) was evaluated by accounting the blocking factor.

Analysis Of The Variability Of Biokinetic Model Parameters Due To Inter-Individual Variation

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Biokinetic models for the assessment of individual internal doses represent the physiological processes of a standardised human which affect the internal distribution of the radionuclide of interest. The flow from one compartment into another is specified by transfer rates, which may vary from person to person. The rate constants are then representing the mean values for the population as a whole, around which individual parameters fluctuate according to given probability densities. Analytical distribution propagation can be calculated only for very simple models. Though the influence of inter-individual variation can be studied with MC simulations, comparing the simulated compartment content distributions using different initial distributions for the parameters. Distributions used were the uniform, the symmetric triangular and the lognormal probability distributions. All parameters were assumed to vary independently with the same coefficient of variation ($cv = \text{standard deviation}/\text{mean}$). Simulations indicate that the form of test distributions affect the distributions of compartment contents only for very simple models in the early stages. Later on (time * transfer rate \gg standard deviation) the distributions converge to a lognormal shape. The cv of the initial distributions can be adjusted that the resulting distributions resemble each other.

Most measurable body parameters (e.g. body size, ...) are lognormal distributed. Due to the lack of significant differences for different parameter distributions, lognormal distributed transfer rates were used for further studies.

The range of inter-subject variability can be estimated by comparing data generated with MC simulations with observed data. For the plutonium model data retrieved long time post intake is most suitable for this purpose when the redistribution of the radionuclide in the compartments is in a state of quasi-equilibrium. Then the retention in each compartment is only determined by excretion rates and thus the ratio of plutonium in different compartments is nearly constant. For the estimation of inter-individual variability the ratios of the main excretion paths (faecal/urinary excretion) and the organs of main burden (skeleton/liver content) can be used. The comparison of observed and simulated standard deviation indicates a value of 0.6 for the cv for all transfer rates. The generated distributions show good agreement with the available data and thus confirm that the MC simulations can represent the inter-individual variation in the biokinetic plutonium model.

Biomaterials for Decorporation of Cobalt-60 in the Rat

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Cobalt-60 (^{60}Co) has long been a problem isotope in the medical management of internal contamination because, while it is always considered to be a possible terrorist agent, no satisfactory medical management is available. The reported investigation is a part of our on-going research program aimed at identifying effective in vivo non-toxic decorporation agents and developing new therapies to mitigate internal contamination with radionuclides. The affinity of cobalt to nitrogen donor chelators is well established. The amino-polysaccharide chitosan exhibited efficient binding of Co(II) in vitro as demonstrated using spectrophotometric and potentiometric titration techniques. For in vivo studies, oral administration of chitosan significantly reduced systemic absorption of ingested ^{60}Co as evidenced by an increase in fecal elimination and decrease in urinary elimination. These results were in agreement with tissue elimination data showing significantly reduced ^{60}Co levels in kidney, liver, and skeleton compared to control animals receiving ^{60}Co alone. For the intravenous (IV) ^{60}Co route, IV chitosan was moderately effective in reduction of radioactivity in tissues compared to controls, and statistically significant reductions were only observed for blood and kidney. The weaker performance of oral chitosan toward internalized ^{60}Co was attributed to its low intestinal absorption and thus insufficient systemic quantities to effectively remove ^{60}Co from the body. Overall, commercially available chitosan exhibited promising potential for chelation therapy. To enhance decorporation of internalized ^{60}Co , biological aminothiols were administered to animals orally or IV following single intravenous injection of ^{60}Co . The obtained results suggest that reduced L-glutathione and L-cysteine are potent decorporation agents for ^{60}Co in the rat model, although the efficacy of treatment depends largely on systemic availability. The IV administrations of L-glutathione or L-cysteine were most effective in reducing tissue ^{60}Co levels and in increasing excretion of radioactivity compared to control animals. Liposomal encapsulation was found to markedly enhance the oral bioavailability of L-glutathione compared to non-formulated L-glutathione. The oral administration of liposomal L-glutathione reduced ^{60}Co levels in nearly all tissues by 12-43% compared to that observed for non-formulated L-glutathione. Efficacy of oral L-cysteine was only slightly reduced in comparison with IV L-cysteine. Further studies to optimize the dosing regimen in order to maximize decorporation efficiency are warranted.

Occupational Dose Assessment of Iodine Intake at ANSTO

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The iodine activity taken up by thyroid is measured by a collimated 7.6x7.6cm NaI crystal, usually following an Iodine incident. To perform a dose assessment of the subject, the ICRP biokinetic retention model, given in ICRP54 publication, is applied to estimate the activity intake in thyroid and whole body. The dose/activity conversion factors from ICRP68 are then applied to obtain the corresponding committed doses (effective & equivalent) of the subject. The 5um AMAD for inhalation route is applied in most cases. Follow up measurements are usually carried out when the Intake exceeds 5 kBq. The results are then compared with the predicted dose by the biokinetic model; adjustment to the model is applied to fit the measured data of individual (if required). The ICRP biokinetic model provides a satisfactory estimate to all encountered cases

Medical Procedure Of A Cutaneous Contamination

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The authors propose a procedure to improve care in the field by medical teams of an incident of cutaneous contamination on healthy skin along two axes: on the one hand, by a synthesis on the practices and the products of decontamination used, and in addition, by making of computer tools intended for the occupational medical doctors. This one will enable them to have a fast dosimetric estimate in the event of contamination of the skin by radioactive particles and to guide them in their diagnostic and therapeutic assumption of responsibility. A standardized sheet of data was created allowing the exhaustive collection of adequate information in order to evaluate the amount skin. The selection of appropriate measuring equipment with a 1 cm² detector, depending on the place and on the surface of the contaminated area allows the evaluation and the quantification of the surface activities. A tool has been realized as a software package, named Cutadose, making it possible to evaluate in the field the skin dose as well as the effectiveness of the resulting therapy.

Radionuclide Decorporation Agent Advanced Development for Use in Radiological Public Health Emergencies: Roles of NIAID and BARDA

Running Title: **Advanced development for radionuclide decorporation agents**

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A radiological/nuclear incident involving the dispersion of radionuclides would require: 1) an immediate critical need to assess the specific radioisotope(s) involved; 2) determination of an individual's level of internal radionuclide contamination; and, 3) the appropriate radionuclide decorporation agent therapy as soon as possible. Decorporation agent therapies are available for select radionuclides, but many current therapies are not suited for use in a large public health emergency scenarios.

Radionuclide decorporation medical countermeasures were identified as a high priority in the publication entitled: *2007 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Implementation Plan for Chemical, Biological, Radiological and Nuclear (CBRN) Threats*. The PHEMCE is an interagency organization led by the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (HHS) to coordinate development, acquisition and provision of critical emergency medical countermeasures to prevent and mitigate the adverse health consequences associated with intentional or accidental CBRN threats and naturally occurring threats. The *PHEMCE Implementation Plan* identifies the top priorities for CBRN medical countermeasure research, development, and acquisition that HHS has determined, in collaboration with interagency partners, to have the greatest potential to improve public health emergency preparedness.

We will describe the roles played by two of the offices within Health and Human Services (HHS), the National Institute for Allergy and Infectious Disease (NIAID) within the National Institutes of Health, and, the Biomedical Advanced Research and Development Authority (BARDA), in the coordination and administration of grants and contracts for early research and development (NIAID) and advanced development (BARDA) of radionuclide decorporation medical countermeasures. Their combined efforts support the PHEMCE goal of providing licensed/approved radionuclide decorporation agents for the Strategic National Stockpile. Using a combination of funding mechanisms as prescribed through Congressional appropriations and legislation enacted for NIAID and BARDA, including funds authorized by the Project BioShield Act of 2004, HHS is enhancing the Nation's preparedness in the field of radionuclide decorporation medical countermeasures by seeking and establishing partnerships with commercial and academic centers of excellence.

Evaluation of Chitosan for Uranium Decorporation in the Rat

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Uranium is a naturally occurring element widely known for its use as fuel in nuclear power reactors and weapons; depleted uranium is used by the military in the conventional war zone. Human exposure to uranium can occur during its mining, processing, environmental contamination, or nuclear/radiological emergency events. Internal exposure to uranium represents a significant health hazard due to its chemical and radiological toxicity and necessitates decorporation treatment. The availability of non-toxic and orally active chelation agents is critical for this treatment. Our preliminary in vitro studies indicate that certain polysaccharides exhibit affinity to uranium under near-physiological conditions. In particular, complex formation between chitosan materials and uranium was observed. Chitosan materials are attractive candidates for decorporation treatments due to their large scale commercial availability, low toxicity, and immuno-stimulating biological activities. In vivo utility of water-soluble chitosan for decorporation of uranium was evaluated using uranium-233 isotope in the rodent animal model. Uranium-233 was administered via single intravenous injection as a standard route of animal exposure to radioisotopes in testing performance of a new decorporation agent. Treatment protocols were designed as a preliminary evaluation and comparison of the efficacy of oral and intravenous (IV) administered chitosan oligosaccharide and its building block, glucosamine. Control animals received uranium-233 without subsequent chelation treatment. Uranium-233 was measured in daily excreta, blood and selected tissues harvested post-mortem at day three post radionuclide exposure. Accelerated uranium elimination and varying reductions of uranium in tissues were observed for treatment animal groups, with the strongest effect seen with immediate IV chitosan treatment. A one-hour delay in IV administration of chitosan resulted in a slight attenuation of its decorporation efficacy. Overall, commercially available chitosan oligosaccharide exhibited highly promising potential for uranium decorporation; further studies are warranted to evaluate the optimal dosing regimen and chemical modifications of chitosan to increase its oral effectiveness.

Tracy U: The French Cohort Of Uranium Cycle Workers

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Objective: To set up a longitudinal cohort for investigating the risk of mortality from cancer and non cancer diseases in relation to uranium and other occupational exposures.

Methods: Primary, ethical approvals of the study protocol and workers consents were looked for. All workers involved in the French nuclear fuel cycle, employed by AREVA group establishments and their subcontractors, and by the French Atomic Energy Commission (CEA), were potentially eligible. The cohort was limited to workers employed for at least one year and working between 1975 and 2006. Retrospective historical data on occupational exposure and individual measurements, such as urinalyses for internal doses assessment and external radiation exposure, were searched from workers' personal medical files. Moreover, the feasibility of gathering individual risk factors data, such as tobacco consumption, blood pressure, and other biological data is led. As a complementary approach, plant-specific job-exposure matrixes should be developed to assure the completeness of data on associated exposures (chemical and physical hazards). Vital status and causes of death will be collected from the French Physical Persons Identification file and the French National Mortality register.

Results: All necessary permissions to conduct the study have been obtained and the data collection is ongoing. Identification and administrative information had been collected for workers employed at Comurhex (UF4 and UF6 conversion: n=1,995), Eurodif (uranium enrichment: n=2,267), AREVA NC (uranium enrichment, chemicals transformation of reprocessed and depleted uranium: n=3,080), FBFC (manufacture of nuclear fuel: n=3,578), CEA (research: n=3,200). For the last company included, Socatri (uranium recovery and cleansing), data collection is ongoing. For the period 1986 to 2004, urinalyses and other biological measurements data were computerized. Historical external dosimetry data were gathered for most of the companies. A job-exposure matrix for the AREVA NC Pierrelatte plant has been performed.

Conclusion: Data collection is well progressed. This cohort will be very informative for the investigation of uranium risk, taking account of multiple exposure patterns of the workers involved in the nuclear fuel cycle. It will also allow investigating non cancer effects in particular cardiovascular risks. As a pilot study, an analyse of uranium exposure effects on cancer mortality was performed among a sub-cohort of the AREVA NC Pierrelatte plant workers: the results are promising.

Physiology Of The Biokinetics Of Plutonium, DTPA And Decorporation Therapy

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Alpha particles emitted by plutonium do not penetrate human skin, but can irradiate internal organs, after plutonium is inhaled, ingested, incorporated by wound or injected. Plutonium is distributed via the blood system and absorbed at bone surfaces and liver. Organs at risk are the skeleton, the liver, the lymph nodes and soft tissues and additionally the lung, when it was inhaled.

Physiology-based compartment models reflect relevant transfers and processes in the body, describing them in a weighted way. In a physiological model, important interactions of e.g. incorporated plutonium, the therapeutic complexing agent Diethylene-Triamine-Pentaacetic Acid (DTPA/used for decorporation of plutonium) and endogenous substances, are described from intake into the body to excretion.

The complexation of DTPA and plutonium mainly takes place in the extracellular fluids, which consist of interstitial water, plasma water of the blood and transcellular water. The biodistribution of relevant molecules in the extracellular fluids of blood, interstitium and lymph was studied first and allows to interpret existing biokinetic models in a physiological way with respect to creating more realistic biokinetic and decorporation models.

Ingestion Of Ra-226 From Activated Paints On Military Equipment: Transfer Factors And Doses

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The use of Ra-226-activated paints on scales, knobs and switches was common on specific military equipment some decades ago. Due to requests for compensations of malignant diseases claimed to be acquired occupationally on military workplaces in the 1960s, the former workplaces with their equipment have to be evaluated in order to specify the extent of possible ingestions and follow-up doses. It is noted that retrospective dose assessments with individual whole- or partial-body counters still lack sensitivity - even with optimized detector geometry- due to the limited retention time of radium in bone as compared to the time elapsed after the possible ingestion.

In this investigation the transfer factors for Ra-226-activities from a marking to skin and from skin to skin are measured by wipe tests on markings on knobs and switches which were taken from decommissioned military equipment. As skin equivalent wipe material pads from ventral pig skin were used. The measurements comprise also wipe tests with linen pads for comparison. The wipe tests were performed subsequently with up to 256 repetitions as well as with waiting times of several days between wipes in order to account for different scenarios of use.

With conservative assumptions on the operation of the switches and knobs and on the transfer the ingested Ra-226-activity is estimated. The effective dose as well as the maximum organ dose on the bone surface are calculated.

Calixarene Nanoemulsion: A New Treatment For Uranium Skin Contamination

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Despite that protection means have been implemented in the nuclear industry, some internal contamination cases of workers by actinides such as uranium may occur either by inhalation, ingestion or penetration through wounds or intact skin. After cutaneous contamination, no specific emergency treatment exists although such cases may induce a high internal exposure to actinides. In this context, we have developed a new topical formulation dedicated to emergency treatment of uranium skin contamination. Taking into consideration the specific chelation properties of calixarene molecules towards uranium, these molecules were introduced in a topical form for skin delivery. An oil in water (O/W) nanoemulsion containing these calixarenes has been designed. The physico-chemical properties of this nanoemulsion were characterized and its efficiency for uranium extraction was evaluated *in vitro* using an ultrafiltration technique to recover the non-chelated uranium and *ex vivo* in Franz cell using pig ear skin.

The characterization of the calixarene nanoemulsion has been performed by measurements of the oily droplets size, the zeta potential and pH measurements. All these parameters were determined as a function of calixarene concentration. According to the results obtained, calixarene molecules seem to be present at the surface of the oily droplets being potentially available to trap uranyl ions present in an aqueous contamination solution. The *in vitro* evaluation of the calixarene nanoemulsion efficiency in optimized experimental conditions (pH, volumes and calixarene:uranium stoichiometry) showed that more than 80% of uranium can be extracted by the calixarene nanoemulsion from an aqueous contamination solution. Uranium skin contaminations were then performed over 24 hours, on intact pig ear skin samples, using Franz cells system. The application of the calixarene nanoemulsion immediately after the contamination quantitatively (98%) inhibited the uranium cutaneous transfer.

In conclusion, this study has successfully demonstrated the efficiency of the calixarene nanoemulsion which according to our data constitutes a promising system to treat uranium contaminated skin. In prospect, *ex vivo* experiments on excoriated skin samples are in progress in order to determine if the formulation is also efficient in case of uranium contamination due to an injury.

MEDECOR

MEDical DECORporation Software To Assist First Responders, First Receivers And Medical Reach-Back Personnel In Triage, Treatment And Risk Assessment From Internalized Radionuclides

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After a radiological dispersal device (RDD) event, it is possible for radionuclides to enter the human body through inhalation, ingestion, skin and wound absorption. From a health physics perspective, it is important to know the magnitude of the intake to perform dosimetric assessments. From a medical perspective, removal of radionuclides leading to dose aversion (hence risk reduction) is of high importance. The efficacy of medical decorporation strategies is extremely dependant upon the time of treatment delivery after intake. The “golden hour”, or more realistically 3-4 hours, is optimal when attempting to increase removal of radionuclides from extracellular fluids prior to cellular incorporation. To assist medical first response personnel in making timely decisions regarding appropriate treatment delivery modes, it is desirable to have a software tool which compiles existing radionuclide decorporation therapy data and allows a user to perform simple diagnosis leading to potential appropriate decorporation treatment strategies. In its most simple application, the software is a large database of radionuclide decorporation strategies and treatments. The software can also be used in clinical interactive mode, in which the user inputs radionuclide, estimated activity, route of intake and time since exposure. The software makes suggestions as to the urgency of treatment (i.e. triage) and the suggested therapy. Current developments include risk assessment which impacts the potential risk of delivered therapy and resource allocation of therapeutic agents. The software, developed for the Canadian Department of National Defence (DND), is entitled MEDECOR (MEDical DECORporation). The MEDECOR tool was designed for use on both PDA and laptop PC environments. The tool was designed using HTML/Jscript, to allow for ease of portability amongst different computing platforms. This talk will present the features of MEDECOR, and results of testing at a major NATO exercise, and future development of this tool.

A Case-Control Study Of Breast Cancer In Women Living Around Semipalatinsk Nuclear Test Site.

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Objective: To elucidate the risk factors of breast cancer in women residing around Semipalatinsk Nuclear Test Site in Kazakhstan. **Materials and methods:** Women born from 1935 to 1962 and living in the areas adjacent to the SNTS, and diagnosed with primary breast cancer during the years 1980-2007. Interviews using a detailed questionnaire and the Cancer Registry at Oncology Center in Semipalatinsk city and local polyclinics. All in all 536 including 216 cases and 320 controls from the districts of Abay, Boroduliha, Beskaragay, Zhana-Semey and from Semipalatinsk city were included into the study. Cases and controls were matched by age and the place of residence. Questionnaire contained: residential history, social characteristics, reproductive history, history of diseases, family breast cancer and others. Logistic regression in SAS was used for a data analysis. **Results:** There was no statistically significant difference between cases and controls in order to radiation exposure and age at menarche. We observed statistically significant difference between cases and controls for family breast cancer, $P=0.0007$, and marginal difference for age at menarche $P=0.006$ and alcohol drink, $P=0.009$.