BOOK OF ABSTRACTS

SCK•CEN-BA-0041

Symposium

Health Impact of Pre- and Post-natal Irradiation: state-of-the-art".

Brussels, October 07, 2011

SCK•CEN
Boeretang 200
BE-2400 MOL
Belgium
http://www.sckcen.be

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Status: Unclassified

RESTRICTED

Contents

Programme

www.sckcen.be www.fanc.fgov.be www.academieroyale.be

Seminar location

Académie royale des Sciences, des Lettres et des Beaux-Arts de Belgique
Rue ducale 1/ Hertogsstraat 1
1000 Brussels
Tel.: +32 (0)2 550 22 12

Route description

From Brussels Airport: By train to Brussels Central Station.

By train: Brussels Central Station. It takes about ten minutes to walk from Central Station to the Academy House. Alternatively, take the metro.

By metro: Subway station Trone

From Central Station: line 1 to Kunst-Wet (Art-Loi) and there line 2.

From Brussels-North (Noordstation, Bruxelles-Nord): tramway to Rogier and there line 2.

From Brussels-South (Zuidstation, Bruxelles-Midi): line 2.

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Registration fee

Full registration: 80 EUR
Students or retired: 40 EUR

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Online registrations

http://www.sckcen.be/en/Events/SPER_FANC_SCKCEN

Deadline for registrations: 23 September 2011

SCK•CEN STUDIECENTRUM VOOR KERNENERGIE CENTRE D'ETUDE DE L'ENERGIE NUCLEAIRE

FANC AFCN federaal agentschap voor nucleaire controle agence fédérale de contrôle nucléaire

Académie royale des Sciences, des Lettres et des Beaux-Arts de Belgique

Symposium on Health Impact of Pre- and Early Post-natal Irradiation

7 October, 2011 // Académie royale des Sciences, des Lettres et des Beaux-Arts de Belgique // Brussels-Belgium

Scope

The first objective of this symposium is to assess the up-to-date scientific data in the field of radiation-induced risks from an exposure of embryos to ionizing radiation. The potential risks associated with an acute embryonic exposure include essentially prenatal mortality, growth retardation and congenital anomalies, mental retardation, leukemia and cancer. Recent data from radiobiological research showed that the genetic characteristics of the exposed embryos may modulate their radiation sensitivity to some extent. On the other hand, new data from epidemiological studies are raising concern. Those include possible increases in particular congenital anomalies or cognitive effects after exposure of germ cells or embryos to chronic low dose irradiation. Early infancy is also a period of peculiar radiation sensitivity, as illustrated by the large increase in the incidence of thyroid cancer observed among people exposed as children to high levels of radioactive iodine after the Chernobyl accident.
Leading specialists have been asked to deliver lectures in the different fields covered by the symposium.

The second objective of the symposium is to discuss the current data and its potential implications, as well as the needs for future research. This part of the symposium will include a round table discussion between various stakeholders, some of them work outside the radiation protection community (journalists, philosophers, legal experts, ...).

Intended to be both scientifically accurate and yet understandable to an educated non-specialist audience, the symposium will take place at the Royal Academies for Science and the Arts of Belgium, in the heart of Brussels.

Time	Titles	Speakers
08:50 - 09:00	Welcome by Patrick Smeesters	Chair: Patrick Smeesters
09:00 - 09:30	"Effect of ionizing radiation on the developing embryo: the classic view"	Hanane Derradji
09:30 - 10:15	"Exposure of early embryos to chemicals and ionizing radiation: the dogma of Teratology revisited?"	Paul Jacquet
10:15 - 10:45	Coffee break	Chair: Hans Vanmarcke
10:45 - 11:15	"In utero irradiation and cognitive effects: recent animal experiments"	Rafi Benotmane
11:15 - 12:00	"Prenatal exposure to ionizing radiation and cognitive effects in humans"	Marten Palme
12:00 - 12:45	"Neural tube defects and other malformations in Ukraine"	Wladimir Wertelecki
12:45 - 14:00	Walking lunch	Chair: Petra Willems
14:00 - 14:45	"Childhood and adult cancer after intra-uterine exposure to ionizing radiation"	Elisabeth Cardis
14:45 - 15:15	"Diagnostic X-ray exposure and DNA damage in children: bystander effects?"	Hubert Thierens
15:15 - 15:45	Coffee break	Chair: Paul Jacquet
15:45 - 16:30	"Genomic alterations and thyroid cancer after childhood exposure to radioiodine due to the Chernobyl accident"	Geraldine Thomas
16:30 - 17:15	"In utero irradiation and transgenerational effects: from mice to men?"	Simon Bouffler
17:15 - 18:00	Round table discussion of current evidence, potential implications and research needs	
18:00 - 18.15	Closing summary	Patrick Smeesters
18:15 - 19:00	Cocktail reception	

Targeted audience

Radiologists and other users of sources of ionizing radiation, radiobiologists, nurses, technologists, occupational medical doctors, experts in physical control, radiophysicists, regulators, ...

Effect of ionizing radiation on the developing embryo: the classic view

Hanane Derradji and Paul Jacquet
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The embryonic development can be subdivided into three periods: (1) the preimplantation period, which extends from fertilization to the time when the embryo attaches to the wall of the uterus; (2) the organogenesis period, during which the major organs are developed; (3) the foetal period, during which growth of the newly formed organs takes place. Experiments performed in laboratory animals have shown that each of these periods is characterized by a particular sensitivity to ionizing radiation or other toxic agents. Thus, it is widely believed that an irradiation during the preimplantation period may essentially result in the death of the embryo. Irradiation during the phase of organogenesis may characteristically result in the production of a variety of congenital anomalies. The induction of anomalies depends on the number of damaged cells in the forming organ and will not occur below a certain threshold (100 mGy in the mouse). Irradiation during the foetal period can induce anomalies in the development of the tissues and general or localized growth retardation. The growth retardation induced during this period frequently persists during all the extra-uterine life.

In man, radiation-induced malformations of body structures other than the central nervous system are uncommon. However, exposure of the human conceptus during the last part of pregnancy, the foetal period, may lead to severe mental retardation associated or not with microcephaly (decrease in head diameter). Data obtained in children who had been exposed *in utero* to the A-bombs in Hiroshima and Nagasaki showed that the probability of SMR (severe mental retardation) is essentially zero for an exposure occurring at less than 8 weeks of gestational age, is maximal for an exposure during the period 8-15 weeks and decreases during the period 16-25 weeks. In addition to these effects, some studies have established a link between irradiation *in utero* and the subsequent development of leukaemia and other childhood malignancies. Although being not proved, this risk is now accepted by the most important scientific committees on account of prudence.

Overall, for small doses, the detriment calculated from the risk estimates for the different potential effects on the developing organism appears rather small, in comparison with the natural risks, spontaneously associated with pregnancy.

Exposure of embryos to chemicals and ionizing radiation: the dogma of teratology revisited?

Paul Jacquet

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Classically, lethality has been assumed to represent the main risk of an irradiation of the mammalian embryo during the pre-implantation period. The potential early loss of an (unsuspected) embryo is usually considered as of minor importance, compared to the risk of a newborn baby being malformed. This explains why, too often, no particular precautions are taken to avoid unnecessary exposure of a pre-implantation embryo in women not aware of their pregnancy. However, various results obtained during the 80's and 90's have suggested that, like a number of chemicals, ionizing radiation could induce foetal malformations in some mouse strains, when administered during pre-implantation stages and particularly at the zygote (or "1-cell") stage. The results also suggested that the genetic susceptibility could play a role in the radiation-induced effects. Irradiation of early pre-implantation embryos has also been suggested to induce a genomic instability in the surviving foetuses. Such effect could be of a general nature but was also reported to occur more frequently in malformed foetuses.

Even if embryonic lethality seems to represent, by far, the principal risk associated with an exposure of the very early embryo to ionizing radiation, the above-reported results are of some concern for radiation protection. Therefore, the purpose of research performed during recent years in our laboratory was to investigate in deeper details how individual genetic characteristics may influence the radiation sensitivity of the mammalian embryo during sensitive stages of early pregnancy. The main parameters that were investigated included morphological development, genomic instability and gene expression in the irradiated embryos or their own progeny.

During this talk, we will summarize the results of these various experiments and, based on a deep reexamination of results obtained earlier in our laboratory and elsewhere, to draw general conclusions on the risks of developmental defects and genomic instability from an

exposure of early embryos of various genetic origins to moderate doses of ionizing radiation.

In utero irradiation and cognitive effects: recent animal experiments

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Epidemiological and retrospective studies on individuals who were exposed to ionizing radiation *in utero* after the atomic bombings in Hiroshima and Nagasaki, showed an increased incidence of mental retardation and learning performances. These defects appeared especially when the irradiation occurred between weeks 8 and 15 of gestation, which is a critical time for human embryonic neuronal development. This suggests a higher sensitivity of neurons during their early differentiation. Thus, an acute irradiation during pregnancy would selectively damage neuron cells, which at that particular time of exposure, are proliferating or migrating.

Previous experiments at the Radiobiology laboratory at SCK•CEN showed that young adult mice that had been exposed to irradiation doses equal to (1 Gy) *in utero* at gestation day (E12) suffered from memory and learning defects as assessed by Morris Water Maze testing. Molecular Resonnance Imaging 'MRI' was performed at different intervals after birth and showed large ventricular zones comparable to hydrocephaly in humans. Gene expression data on brain of embryos irradiated with the same dose showed induction of stress-related genes, in particular the P53 pathway involved in cell-cycle arrest and apoptosis ("programmed cell death"). Further experiments are planned to confirm the induction of apoptosis in the brain at early embryogenesis, which would correlate perfectly with the imaging data. In parallel, *in vitro* culture of primary neuron cells has been optimized in order to monitor the effect of low doses of radiation during neuron maturation. Neuron cells exhibit a shortening in the length of neurite and a decrease in the number of neurites per neuron after irradiation at early stages of their maturation. At later stages, branching of neurites appears to be prevented by radiation, and neuron degeneration is observed when irradiation occurs during synaptogenesis or during neural network formation (neuronal connectivity).

Taken together, irradiation at early stages of brain development at the critical period of neurogenesis would interfere at two different levels, first by inducing apoptosis reducing

dramatically the neuronal cell mass and second by affecting neurite outgrowth and neuronal connectivity. Both aspects should interfere with normal neural network formation, leading most probably to adult behavioural and cognitive disorders.

Prenatal exposure to ionizing radiation and cognitive effects in humans

Marten Palme

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Epidemiological studies of A-bomb survivors have shown that prenatal irradiation 8-25 weeks post conception affects cognitive development. Radioactive fallout from the Chernobyl reactor meltdown in 1986 travelled widely and provides a natural experiment for evaluating whether fetal exposure to low-level ionizing radiation (estimated below 3 mSv in Sweden) had long-term cognitive impacts. Using a dataset of school outcomes for 562,637 Swedes born in the mid-1980s, we employ empirical techniques common in applied economics for the evaluation of non-experimental data. Consistent with the A-bomb studies, we find that the cohort *in utero* during the Chernobyl accident has worse school outcomes than adjacent birth cohorts, and that this deterioration is largest for those at weeks 8-25 of gestation, when neural development is most rapid. We also evaluate whether: (a) the magnitude of damage corresponds to the substantial geographic variation in fallout across Sweden, and; (b) whether those exposed at weeks 8-25 of gestation had worse academic outcomes than their siblings. Each of these distinct tests indicates that the Chernobyl accident impaired academic performance in Sweden. Students from the eight most affected municipalities were 3.3 percentage points (30 percent) more likely to fail a core subject as a result of the fallout. Our results demonstrate that damage to cognitive ability likely occurs at radiation levels previously considered safe.

A Chornobyl Impacted Population Isolate in Ukraine
High Rates of Neural Malformations
Call for International Research Co-investigations

Wladimir Wertelecki

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Background: In 2000, OMNI-Net (a not-for-profit international organization registered in Kyiv and initiated with international assistance), established a birth and a congenital malformations (CM) population registries in Ukraine relying on methods used by a European network of CM monitoring systems (EUROCAT); in 2002, elevated rates of neural tube defects (NTD) were noted and confirmed by an analysis of 2000-2006 data. Population rates of microcephaly (MIC), a-micro-phthalmia (MOPH), and probably teratomas (TER), and conjoined twins (CTW) were also found to be elevated. Concurrently, these rates were noted to be higher in the Rivne Polissia region (Prypiat river marshes), consisting of the 7 northern counties of the province. Six Rivne counties are officially designated as Chornobyl Ionizing Radiation (CIR) impacted and all six are in the Polissia region. Polishchuks, the native inhabitants of Polissia, represent a Ukrainian ethnic sub-group with characteristics of a population isolate.

Goal: to determine population malformation rates including in severely impacted Chornobyl regions.

Objectives: to document and analyze population CM rates, temporal trends and to test strategies and feasibility to sub-categorize regions by county, village, family groups and levels of external and internal exposures to CIR (inhalation, ingestion, whole body CIR counts), life-style (alcohol use, nutrition, occupation, dwelling), and isonomy levels (frequency of shared family surnames) characteristic of settlements in the investigated regions as a proxy measurement of consanguinity and shared environments.

Results: analyses of 145,437 live-births from 2000 to 2009 demonstrate persisting elevated population rates (per 10,000 live births) of NTD, microcephaly and a-micro-phthalmos. These rates are significantly higher in Polissia vs. nonPolissia (26.1-16.4; 5.7-3.3; 2.9-1.1 respectively) and also are among the highest in Europe. Within Rivne, the highest NTD and MIC+MOPH rates were noted in vicinities of two nuclear power plants (34.1-31.9; 12.2-11.2 respectively) but the number of observations are few and preliminary. The birth of 8 CTW twin pairs and occurrence of 11 TER (both are rare anomalies) suggests an excess. Regarding known causes of neural CM, CIR levels in soil, milk, and whole body counts obtained from ambulatory patients and pregnant women were highest in the 3 most northern Polissia

counties (NP). Consumption of alcohol by pregnant women, one of the major causes of microcephaly, was less frequent in Polissia than in nonPolissia. Regarding genomic factors, family surname isonomy levels were highest in NP.

Conclusions: these observations are sufficiently compelling to call for case-control or other prospective investigations with an emphasis on NP families. Further categorizations of NP village populations by life-style, levels of IR, including WBC, along with degrees of isonomy or other estimates of consanguinity can contribute to clarify the relative impacts of CIR, alcohol and genomic factors causing the elevated CM rates observed. Three Ukrainian Provincial Public Health authorities from the impacted regions and the Research Center for Radiation Medicine of the Ukrainian Academy of Medical Sciences and OMNI-Net have issued a ***call for international research co-investigations***.

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Childhood and adult cancer alter intrauterine exposure to ionising radiation

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Little epidemiological information is available about the magnitude of cancer risk following *in utero* exposure to ionising radiation. Large scales studies of patients exposed *in utero* from X-ray pelvimetry have shown an increased risk of childhood cancers following very low doses of radiation, though the exact magnitude of this effect is uncertain. Information is also available from studies of smaller cohorts in Japan (*in-utero* cohort of the atomic bomb survivors) and Northern Ukraine (offspring of a cohort of mothers who were pregnant at the time of the Chernobyl accident in the Northern region of Ukraine).

While an increased risk of cancer is apparent in most cohorts, it is at present unclear whether this increase is larger or of a similar magnitude to that of children exposed in the first years of life.

Diagnostic X-ray exposure and DNA damage in children: bystander effects ?

Hubert Thierens

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A better knowledge of patient X-ray dose and the associated radiation risk in pediatric radiology is indicated in view of the higher radiosensitivity of children. A study was performed of X-ray doses and effects in pediatric patients undergoing interventional cardiology procedures [1]. DNA double strand breaks (DSBs) in peripheral blood lymphocytes assessed by scoring γ-H2AX foci were used as biomarker for radiation induced effects.

In 49 pediatric patients (median age: 0.75 y) with congenital heart disease, who underwent cardiac catheterization procedures, blood samples were taken before and shortly after the procedure and γ-H2AX foci were determined in peripheral blood T-lymphocytes. For each patient a net increase of γ-H2AX foci, representing DNA DSBs induced by interventional X-rays, was observed. In addition, a patient-specific Monte Carlo simulation of the procedure was performed, resulting in individual blood, organ and tissue doses. Plotting of γ-H2AX foci versus blood dose revealed a low-dose hypersensitivity. Median effective dose calculated according to ICRP 103 publication was 6.4 mSv.. The risk of exposure induced death (REID) was calculated based on the LNT model and the γ-H2AX foci data. This resulted in REID values of 1 ‰ and 4 ‰ respectively for the patient population under study.

In vitro irradiation of blood samples resulted in a biphasic dose response with a low dose hypersensitivity for γ-H2AX foci scored in T-lymphocytes. This biphasic behavior with low dose hypersensitivity was also observed for phosphorylated ATM foci in *in vitro* irradiated primary human lung fibroblasts (MRC-5) [2]. When cultures are treated with lindane a gap junction intercellular communication inhibitor the dose response is linear and the low dose hypersensitivity disappears indicating that bystander effects are responsible for the low dose hypersensitivity.

The oncogenic potential of DNA DSBs induced by the bystander effect was studied in a radiosensitive *Pitch1* mutant mouse animal model [3]. Partial body irradiation of neonatal mice with head and upper body shielded resulted in γ-H2AX foci in the cerebellum induced by the bystander effect. Furthermore 3 Gy partial body irradiation induced medulloblastoma in 39 % of the shielded mice pointing to oncogenic bystander effects Non-targeted radiation effects contribute to carcinogenesis in bystander tissues. These findings are in line with observations

that secondary solid cancers in patients treated for childhood cancer are located for a large part close but outside the treatment volume [4].

These studies support that the LNT estimation is not necessary a conservative upper limit of radiation risk but can also result in an underestimation of risks due to the bystander effect.

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Genomic alterations and thyroid cancer after childhood exposure to radioiodine due to the Chernobyl accident

Geraldine Thomas

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The main consequence of the Chernobyl accident has been an increase in papillary thyroid carcinomas (PTCs) in those exposed to radioactive fallout as young children. The risk appears to be higher in those who were exposed as young children (0-4 years of age), although it is still too early to be certain that this is related to a shorter latency for tumour development in those who were exposed early. The results documented so far suggest that clinically radiation-induced thyroid cancers are similar to those observed in children who were not exposed. Interestingly, the molecular biology of these tumours is distinctly different from that observed in adults. In general, the molecular biology is similar in children whether the tumour has developed as a result of radiation exposure or not. However, recent results suggest that there may be subtle differences related to amplification of a region on 7q. However, these studies need to be further validated, and related to be the dose of radiation received before their true relevance can be elucidated.

In utero irradiation and transgenerational effects: from mice to men

Simon Bouffler

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The risk of hereditary effects in irradiated human populations is estimated from experimental mouse studies of germ line mutation. No direct human data on the hereditary effects of radiation exposure are available. Since the 1990s, DNA repeat sequence markers have been used to investigate germ line mutation and transgenerational mutation in humans and experimental animals. Some such studies have identified transgenerational effects following *in utero* and adult irradiation. Consistent evidence for such phenomena in humans is lacking. Experimental studies are now beginning to show that the observed transgenerational effects may be mediated by persistent and transmissible changes to gene expression caused by epigenetic modification of the genome. The understanding of epigenetic changes such as DNA methylation and histone acetylation are beginning to reveal how the environment can affect the genome to modify phenotypes and disease risk.