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Genomic damage in children accidentally exposed to ionizing radiation: a review of the literature.

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Layout

Abstract

During the last decade, our knowledge of the mechanisms by which children respond to exposures to physical and chemical agents present in the environment, has significantly increased. Results of recent projects and programmes focused on children's health underline a specific vulnerability of children to environmental genotoxicants. Environmental research on children predominantly investigates the health effects of air pollution while effects from radiation exposure deserve more attention. The main sources of knowledge on genome damage of children exposed to radiation are studies performed after the Chernobyl nuclear plant accident in 1986. The present review presents and discusses data collected from papers analysing genome damage in children environmentally exposed to ionizing radiation. Overall, the evidence from the studies conducted following the Chernobyl accident, nuclear tests, environmental radiation pollution and indoor accidental contamination reveals consistently increased chromosome aberration and micronuclei frequency in exposed than in referent children.

Future research in this area should be focused on studies providing information on: (a) Effects on children caused by low doses of radiation; (b) effects on children from combined exposure to low doses of radiation and chemical agents from food, water and air; and (c) specific effects from exposure during early childhood (radioisotopes from water, radon in homes). Special consideration should also be given to a possible impact of a radiochemical environment to the development of an adaptive response for genomic damage. Interactive databases should be developed to provide integration of cytogenetic data, childhood cancer registry data and information on environmental contamination. The overall aim is to introduce timely and efficient preventive measures, by means of a better knowledge of the early and delayed health effects in children resulting from radiation exposure.

Key words: child, ionizing radiation, environment, chromosome aberration assay, micronucleus assay, Chernobyl

Introduction

The cancer incidence in children has increased during the last few decades in different parts of the world [1, 2]. The present occurrence per year is a 1% average annual increase in incidence ($p < 0{\cdot}0001$) has been estimated from the European cancer incidence database, including some 110,000 childhood cancer cases from 63 population based registries [1]. Although this increase may partly reflect better diagnostics, its aetiology is probably also associated with parental, intrauterine and postnatal exposure to xenobiotics including low LET ionizing radiation (e.g., X-rays and γ-rays). [**3]**

Indeed, the occurrence of site specific cancer in children is different than in adults, suggesting that childhood cancers reflect foetal development and exposure [4,5].

Children live in complex radiochemical environments and share all types of exposures with their parents [Figure 1]. Over the last few decades genotoxicological population studies have mostly focused on occupational exposures. Exceptions were cases of accidental exposure of the general population, including children. Recently, genotoxicologists have paid increasing interest in studies of children addressing the issue of whether they are more susceptible to environmental exposures to physical and chemical agents than adults [6, 7,8].

Based on the available evidence of quantitative health risks associated with radiation exposure, public dose limits of exposure from mining or nuclear plants are currently set at 1mSv/yr above background [9], but still there is no specific legislation concerning children, although such exists for occupational exposure during pregnancy [10].

Except for a few studies of children after accidental overexposures, available data on the consequences of radiation exposure in children are mostly limited to the monitoring of young victims following April 26, 1986 when the world's worst nuclear power accident occurred at Chernobyl in the former USSR (now Ukraine). The Chernobyl nuclear disaster affected a vast area of Europe and may still contribute to genome damage in large areas of Ukraine and Belarus due to the environmental persistence of some radionuclides [11].). Information on genome damage caused

by radiation from this and also other nuclear accidents in the former Soviet Union is, however, only partially available to the scientific community, because scientists of the former USSR still publish in national rather than international journals.

Sixty years ago in Hiroshima and Nagasaki mankind witnessed the first nuclear weapon attack which for the first time in history had transgenerational consequences. The difference in the type of exposure in Hiroshima and Nagasaki versus Chernobyl is that while the nuclear bombing resulted in massive exposure to mixed gamma/neutron radiation, the Chernobyl accident caused an acute exposure, followed by a long-term internal exposure mostly to low doses of gamma radiation [12]. Differences in the type of exposure are reflected in the difference of cancer incidence between these two nuclear disasters. After the Hiroshima and Nagasaki detonation, ionizing radiation-induced leukaemia occurred in children 5 to 6 years later, while in adulthood the breast cancer incidence increased in women who were exposed before puberty [13]. Recent epidemiological reports from Ukraine and Belarus confirm an increased number of cases of thyroid cancer in children, but not leukaemia [12]. Thyroid cancer patients aged 15 or younger lived in the most contaminated regions (the Provinces of Kiev, Chernigov, Zhitomir, Cherkassy, Rovno, and the city of Kiev). The highest reported incidence was in children who were exposed at the age of five years or younger. [14]. However, because of the lack of proper cancer registries in Ukraine and Belarus, and the large number of people evacuated from the polluted areas that could not be traced through any kind of demographic records, these findings are considered to be of limited significance [15]. Moreover, in some regions of Ukraine and Belarus long-term exposure was accompanied by malnutrition, frequent infections and stress, important confounders that may have had strong impacts on the reported genome damage [16].

A systematic overview of available data of genome damage in children environmentally exposed to ionizing radiation is missing. Data from scientific papers written in Russian, Byelorussian and Ukrainian language are not well known in the Western scientific community due to language barriers. The aim of this study is to present and interpret systematically collected data on genome

119 damage in children exposed to ionizing radiation at the global level (cosmic radiation is excluded).
120
121 **Materials and methods**
122 The scientific literature considered here was selected following an extensive literature search
123 without any language restriction by using the Med-Line/PubMed database (National Library of
124 Medicine, National Institutes of Health, Bethesda, MD, USA-http: //www.ncbi.nlm.nih.gov/
125 PubMed) covering the time period between January 1, 1980 and December 30th, 2006. Searches
126 comprised studies of children from newborns to late adolescence (age 0–18 years) exposed to
127 ionizing radiation. We have excluded case reports, studies without a clear definition of exposure to
128 ionizing radiation, studies with less than 10 children and/or lacking a referent (unexposed)
129 population, and studies reporting findings in a conversational style without statistical measures
130 (e.g., mean and standard deviation) or analysis. Studies written in English, Russian, and Ukrainian
131 were retrieved and manually reviewed. Studies that were not accessible through online library
132 systems were obtained by the authors or through interlibrary exchange. Twenty East European
133 studies of children not available in English but with important information have been recognised
134 and included in this review. Information about these studies can be obtained upon request. Results
135 from the following assays of genetic toxicology were considered: chromosome aberration assay
136 (CA), *in vivo* and *in vitro* micronucleus assay (MN), comet assay, sister chromatid exchange (SCE),
137 and fluorescent in situ hybridization (FISH). In order to simplify the presentation and the
138 interpretation of the reviewed studies the association between radiation exposure and biomarkers of
139 DNA damage in children was quantitatively investigated by computing study specific ratios (MRs)
140 of the mean level of each biomarker detected in radiation exposed and in referent children or
141 newborns. The computed MR is a point estimate of the relative effect of the exposure on biomarker
142 level detected in each study taking the value 1 (MR=1) when there is no effect of radiation exposure
143 on biomarkers level, values greater than 1 (MR>1) or lower than 1 (MR<1) when radiation
144 exposure is associated with an increased or a decreased levels of the investigated biomarkers,

145 respectively. The MR, as a measure of effect, has the advantage of being independent of the
146 absolute values of the biomarker mean levels reported by the single studies and is comparable
147 across the studies and endpoints considered. The main characteristics of the studies considered in
148 this paper including their findings and the computed MRs, are summarized in Tables 1-3.
149
150 **Results**
151 **Exposure to ionizing radiation from natural sources**
152 Naturally-occurring radionuclides in food and water are primarily potassium (^{40}K) and the decay
153 products of Uranium (^{238}U), Thorium (^{232}Th), Carbon (^{14}C) and Rubidium (^{87}Rb) [17]. Radium
154 (^{226}Ra, decay product of ^{238}U in nature) decays into radon (^{219}Rn, ^{220}Rn, and the most stable radon
155 isotope ^{222}Rn, with half life 3.82 days) which is emitted as a gas in significant quantities and can
156 reach levels in indoor air up to 15,000 Bq/m^3. The main intake of ^{222}Rn is via drinking and
157 breathing. The European regulations and US environmental action levels are 150-200 Bq/m^3 [18,
158 19, 20,21].
159 A possible association of radon exposure with adverse health effects, including lung cancer
160 development, has been recognized relatively recently [22, 23]. Critical environments are poorly
161 ventilated old dwellings built in karsts-rich areas, geographical areas of irregular limestone where
162 erosion has produced fissures, caverns and underground streams. Children may be exposed to radon
163 at kindergarten, school and at home. An additional (although less important) source of exposure to
164 radon could also be building material such as certain types of concrete and granite tiles [24].
165 Rommens et al 2001 [25] reported European ionizing radiation exposure levels of 2.4 mSv/y for
166 adults, 2.7 mSv/y for children and 5,4 mSv/y for infants 0-1 years old taking into account all natural
167 sources such as ^{222}Rn and ^{220}Rn (decay product of thorium, commonly named thoron), cosmic
168 radiation, terrestrial radiation, radionuclides, etc. The total body concentration of radionuclides and
169 equivalent doses to red bone marrow is age dependent and is higher in children, especially in infants
170 and adolescents for ^{226}Ra, lead (^{210}Pb), ^{228}Th, Polonium (^{210}Po), etc [25, 26,27].

As radon daughter products follow the metabolic pathway of calcium, its incorporation into children's skeleton poses a significant health risk [28]. Due to age dependent developmental stage of the gastrointestinal system of children, the highest absorption of radon is in newborns and in children between 13 and 17 years of age [27,29]. This is accompanied with high water intake in newborns and children in comparison with adults [30]. Children and adolescents are target populations for intake of water which can be radiocontaminated, due to the increased usage of bottled water in Europe and its use for production of a number of different drinks favoured by the youngest. The increased effective dose from radiocontaminated mineral water may be up to seven times higher in infants and teens than the maximum level recommended by the World Health Organization (100 μSv,) [31]. It has been suggested that this exposure may be specifically relevant for the hormonal activity of testosterone and oestrogen during puberty when final maturation of skeleton occurs [32]. Non breast fed infants less than 1 year of age may receive doses up to 0.28 mSv/y if their diet is exclusively prepared with mineral water with elevated radon concentrations from ^{226}Ra decay [33]. In addition, such waters contain other radionuclides such as ^{210}Pb and ^{222}Ra also contributing to the total received dose [33].

The health risk related to indoor radon exposure is still a subject of discussion. It has been shown that residential radon exposure may contribute to increased cancer incidence. The average radon exposure of 50 Bqm^{-3} has been estimated to be responsible for 13-25% of myeloid leukaemia cases at all ages [34,35]. Indoor exposure at an annual dose of 7-11 mSv from radon has been reported to be associated with a significantly increased frequency of chromosome aberrations (MR=1.69, Table 1) and micronuclei (MR=1.44, Table 2) in children [36]. To decrease radon levels in the working and living environment some countries have established programmes for remediation work in buildings, primarily schools and homes [37].

Exposure to high-dose ionizing radiation

The Chernobyl nuclear accident.

After the 1986 Chernobyl nuclear power plant accident, populations of Ukraine, Belarus and Russia were exposed to Iodine (^{131}I), Caesium (^{137}Cs, ^{134}Cs), Strontium (^{90}Sr) and to a wide spectrum of short-lived isotopes which were not measured by physical dosimetry [11]. Later on, exposure became continuous with constant intake of radionuclides via food and water, including ^{90}Sr which is incorporated in the skeleton of children at 4-6 fold higher rates than in adults [38]. It has been estimated that following the Chernobyl accident approximately 160,000 children aged 7 years or less were exposed to a variety of radioactive isotopes [39]. The explosion of the Chernobyl-4 reactor core led to the release of radioactivity that was deposited in the surrounding area as dust and debris, while the lighter material was carried by wind over the Ukraine, Belarus, Russia and to some extent over Europe, with radioactive fallout in Scandinavia, Austria and Switzerland [17]. Some 15 to 23 kg of plutonium were released, the majority within an area of 80 km radius around the nuclear plant [40]. Immediately after the accident, a first zone with more than 40 Ci/km^2 (the 10 km range zone) and a second one with more than 15 Ci/km^2 (range of 30 km) were identified. A third area of 145,000 km^2 was contaminated with more than 1 Ci/km^2. After the accident 135,000 people were evacuated from the first zone and after some time 210,000 more subjects were evacuated. An unidentified number of evacuated subjects were sent to different parts of Russia, Israel or other European countries, for varying periods of time. Today, about 3.8 million people live in the area with more than 1 Ci/km^2. The effective human annual dose is in the range between 54 μSv and 3.1 mSv [41, 42]. Efforts to reduce the exposure of the population through altering their diet were not very successful [40]. In affected area increased incidence of thyroid cancer in children [43] and recently breast cancer have been reported [26, 27]. Breast cancer could be expected to follow thyroid cancer since the mammary gland is derived embryogenetically from primitive iodide-concentrating ectoderm [26, 30, 44, 45, 46]

***Chromosome aberrations*.** Cytogenetic studies of the children population in Ukraine started in 1988

221 [47]. Studies reported in [47] were performed on peripheral lymphocytes and only *in vivo* MN assay
222 was performed on reticulocytes. Results revealed dose-dependent increased levels of CA, with MRs
223 of 3.22 and 1.98, in children exposed to ^{137}Cs at levels between 18 and 55 x $10^{10}Bq/km^2$ and lower
224 than 1 x10^{10} Bq/km^2, respectively (Table 1). Repeated measurements of chromosome aberrations
225 within a 4 year period after accidental overexposure in children living in contaminated areas [48]
226 revealed a 53% increased average level of genome damage as measured by the chromosome
227 aberration (CA) assay (Table 1). The follow-up of several exposed and evacuated groups of
228 children born before and after the nuclear accident by highly experienced cytogenetic centres such
229 as those in St. Petersburg (Russia) or in Pisa (Italy) also showed the persistence of the genome
230 damage. Anage related radiosensitivity was detected in children from Belarus who were sampled
231 three months after the Chernobyl accident. A significant difference was found in the number of
232 dicentrics between young (6-10 years) and older (11-15 years) children (Table1), with 1.17% and
233 0.67% dicentrics, respectively [49]**.** Up to 10 years after the accident children were still suffering
234 from internal contamination: CA frequencies were up to 4 times higher in exposed than in reference
235 children (Table 1) [50, 51, 52, 53]. In exposed children the frequency of dicentrics was 0.44%
236 compared to 0.02% observed in unexposed children (Table 1) [54]. Such an alarming situation
237 feeds speculations about an accumulation of stable genome damage in these children and potentially
238 related adverse health effects that may occur later in life. Cytogenetic studies also showed that even
239 the areas which are considered as unpolluted are actually contaminated with radionuclides at levels
240 that are capable of increasing genome damage in children [47]. The impact of internal
241 contamination was seen as a presence of rogue cells (specific type of multiaberrant cells) detected
242 in children living in contaminated areas [55]. In this study 328 Belarussian children were analysed
243 by the CA assay. The majority of the children (321 subjects) were exposed postnatally. In six
244 children exposed *in utero* one or two rogue cells were detected in 200 analysed metaphases.
245 Detected rogue cells contained up to 9 dicentrics, up to three tricentrics or/and rings and
246 quadricentrics.

***In utero exposure*.** The Chernobyl accident affected also pregnant women who were exposed to different levels of radiation before being evacuated. A study using G banding was performed on two groups of children exposed *in utero* and during childhood to ionizing radiation [56]. Children born by mothers who were pregnant at the time of the accident and evacuated shortly afterwards were exposed to radiation levels ranging between 10 and 376 mSv while children exposed *in utero* and chronically during the childhood experienced a cumulative dose of 19-52 mSv. An increased frequency of CA was detected in newborns from both groups of women. As shown in Table 1 mean frequencies of 9.07% ±1.34 and 7.63%±2.92 of CA were measured in the group of intrauterine exposed children and in children exposed *in utero* and after birth, respectively, compared to a frequency of 2.47%±0.4 detected in referent children (MR= 3.67 and 3.08). Translocations, inversions and deletions represented almost 80% and 70% of chromosome type aberrations in intrauterine exposed and continuously exposed children, respectively [56]. Non random distribution of chromosome damage was detected: the most frequently involved chromosomes were chromosome 1, 3, 5, 7, 9, 11, 13, 21 and 22 [56]. On the background of the available scientific evidence, this predominant localization of break points correlates with diagnostics markers of neoplastic disease as summarized in Table 4 [57]. All detected bands at which chromosome breakage was present are non-random and related with the described neoplasias.

***Parental exposure*.** A high frequency of aberrant cells (1.12± 0.37%) was measured in children exposed *in utero* to 2.0-2.5 cSv, in those born between 1987-1991 (1.24±0.4) as well as in children born between 1994-1998 (1±0.2) compared to children born before the Chernobyl accident (0.59± 0.3%), with MRs of 1.90, 2.1, and 1.69, respectively [58].A long-term follow-up study of populations living in a contaminated area of 15, Ci/km^2 [58] showed increased genome damage in children of irradiated parents (Table 1). The highest frequency of aberrant cells (1.24± 0.4%) was measured in children born by mothers who were continuously exposed to ionizing radiation following the Chernobyl accident (MR=2.1).

The paternal transferability of possible genome damage has been investigated in children born after

their fathers were exposed as liquidators at the Chernobyl nuclear plant. Genome damage was measured in 15 children born after evacuation using the CA assay [59]. A clear increase in CA (MR=1.64, Table 1) was detected in children of Chernobyl liquidators who suffered with radiation burns of 1st and 2nd degree (2.38%±1.9) compared to referents (1.45%±0.2).

Six years after the accident children who were evacuated at different times following the accident and children born after cessation of their father's exposure were analysed for CA. Evacuated children had spent between 2 days and 2 years in contaminated areas. As it is shown in Table 1, clearly increased frequencies of CA were detected in children of exposed liquidators (2.8%±0.2) and in evacuated children (2.5%±0.1) compared to referents (1.8%±0.2). Noteworthy, evacuated children still had almost ten times more dicentric and ring chromosomes than controls (0.19% and 0.02%, respectively, data not shown). Such increased values of these types of CA could reflect genomic instability, a phenomenon of increased rate of acquisition of alterations in the mammalian genome proposed to be a driving force in carcinogenesis [53]. Indeed, germline mutation frequencies at human minisatellite loci among children born in polluted area and receiving doses of about 0.18 Gy were shown [60] to be two times higher when compared with a control population (mutation rate per band 0.03 versus 0.01, respectively). The measurement of new fragments using multi-site DNA fingerprinting showed that liquidators' children born after the Chernobyl accident had a seven-fold increased level of new bands that were not present in their sibs conceived before the Chernobyl accident [61, 62].

Micronucleous Assay, Comet Assay, FISH, and SCE. Among the *in vitro* studies conducted on children exposed following the Chernobyl accident (Table 2), the one by Mikhalevich et al 2000 [49] failed to detect a difference in the frequency of MN in binucleated lymphocytes of those living in contaminated areas for 9 years after the accident and being chronically irradiated by internal contamination, compared to referents (MR=0.83). The study reported a clearly increased frequency of MN in mononucleated lymphocytes (MR=2.48) in chronically irradiated children (Table 2). Two studies [63,64] reported a twofold increased frequency of micronucleated cells in radiation exposed

compared to referent children while another [65] detected similar levels of micronuclei in exposed and referents (Table 2). Using the *in vivo* micronucleus assay, liquidators from Chernobyl and their children evacuated following the nuclear accident [66] were observed to express significantly increased mean micronuclei levels in peripheral lymphocytes compared to referent children (0.19‰ and 0.012‰ micronucleated cells, respectively, MR=15.8). This is the only available study on a population environmentally exposed to radiation monitored by the *in vivo* MN assay.

The Comet assay has been used to estimate genome damage levels in children from Belarus 10 years after the Chernobyl accident [67]. An increased genome damage was still present in their lymphocytes (Table 3), a finding that could be explained as a "clastogenic factor" present in 19% of these children [67]. When the translocation frequency was measured using FISH (Table 3) in a group of exposed children and in age matched referents, higher levels of translocation were found in the former (0.65%±0.1) than in the latter group (0.14%±0.05) corresponding to an MR of 4.64 [68]. In the same study higher MN frequencies were found in exposed children than in exposed adults (0.06‰), a finding that is suggestive of a higher sensitivity of children to ionising radiation induced cytogenetic damage, since it seems unlikely that the children were exposed to higher levels of radiation than their parents.

Antioxidants and lipid peroxidation.

Several studies (not included in any table) have investigated the association between radiation exposure, lipid peroxidation disorders, and cytogenetic damage. Analyses of children born by mothers who were exposed to low doses of radiation before pregnancy showed that in regions contaminated by radionuclides, these children suffered from lipoperoxidase disorders and that the levels of essential antioxidants such as vitamin A and E were low. For mothers on a diet supplemented with these vitamins during pregnancy, the chromosome aberration frequency in their newborns was significantly lower in comparison with children born by mothers without such vitamin supplemented diet [69]. The complexity of interaction between the organism in development and radiation is also illustrated by a bimodal pattern of distribution of the gluthatione

system [70, 71] in children born by mothers exposed to different dose levels. In children born by mothers exposed to doses between 0.8 and 30 cSv, increased levels of reduced plasma glutathione (up to 90 μM) could be detected, while in mothers exposed to doses between 30 cSv and 60 cSv, severe decrease (5 μM) was detected. Gluthatione mediates a reduction of at least two vitamins, alfa-tocopherol and ascorbic acid which are critical in prevention of lipid peroxidation. Additional consequences of exposure to ionizing radiation and disturbances of glutathione level are seen in cases of combined radiochemical exposure. Increased levels of polycyclic aromatic carbons (PAH)-DNA adducts are found in human placenta of mothers exposed to both ionizing radiation and environmental PAH, suggesting a possibly higher health risk for the foetus in a case of complex exposure than would be expected exclusively from PAH concentrations in air [72].

Radiation induced adaptive response.

An adaptive response of subjects exposed to low doses of chemical agents or radiation has frequently been investigated by Russian and Ukrainian scientists. The existence of radiation associated hormesis (i.e. the concept that small doses of radiation may reduce the damage to levels even lower than those observed in unexposed controls) is still debated in the literature. The adaptive response is a characteristic feature of both mammalian and plant cells in their response to various mutagenic agents [73]. This phenomenon occurs when cells are treated with a low dose of a clastogen; such a pre-treatment may then reduce the effect of a subsequent treatment with a higher dose of the same or a similar agent (the challenging treatment). Adaptation can be measured by the challenge assay in which lymphocytes isolated from exposed and control subjects are treated with either 1 Gy or a combination of 0.05 Gy and 1 Gy. Compared to children living in Moscow's urban polluted areas, increased micronuclei frequencies were reported among children from the Chernobyl area exposed to radiation by living in areas with contamination levels ranging between 5 and 40 Ci/km^2. Lymphocytes of children from these radiocontaminated areas showed increased frequencies of chromosome aberrations and micronuclei in the challenge assay, suggesting that, in this exposed population, subjects express a radiosensitivity with no indication of an adaptive response. These

results may show that a routine application of chromosome aberration and/or micronucleus assay without also employing a challenge assay may not be sufficient for the detection of genomic instability [63]. By comparing this radiosensitivity with the observations of adaptive response in the adult and children populations from Ural (internal exposure with ^{90}Sr from the Techa River) and the Chernobyl regions, some common features were apparent. In both groups of exposed children, individuals with high radiosensitivity were recognized after a challenging dose of 1 Gy and using MN as the endpoint. Among referent children from the Moscow region, inter-individual differences in MN frequencies were significantly lower after challenge assay than in exposed group. Based on such sada It is suggested that adaptive response is not developed and will not be expressed in adulthood if a person is exposed as a child to elevated levels of radiation or other xenobiotics [74, 75].

Hiroshima and Nagasaki

The Chernobyl disaster resulted primarily in radiation via internal contamination, whereas after the Hiroshima and Nagasaki bombings the primary source was gamma radiation and fast neutrons. This represents different types of exposures, which are also associated with different cancer incidence distributions [76]. Two to three years after the bombing, leukemia was the first cancer to be linked with exposure with the highest incidence of leukemia detected in people exposed during their childhood [77]. Besides the increase in leukemia, elevated rates of solid cancers such as cancers of the breast, lung, and colon have been reported which seem to be larger among subjects exposed during their childhood than among those exposed as adults [78].

Cytogenetic analyses of exposed populations started 15 years after the bombing [79] due to the fact that cytogenetic methods were not introduced until the 60's. A number of different research teams have been involved in studying health consequences in survivors and studies are still on going among children of exposed subjects. [80]

Nuclear plants

Epidemiological studies have reported clusters and increased risks of leukaemia in subjects living in areas adjacent to nuclear power plants [81, 82, 83, 84, 85, 86, 87, 88]. A significant excess of leukaemia cases in the general population living in the proximity of nuclear plants has also been reported [82, 89, 90] along with a possible association for children whose father were employed at a nuclear plant [90].

Comment [dfm1]: I've moved refs for krummel here to get rid of reiterations seen by Gunnar

A systematic review of leukemia incidence and mortality cohort studies in children living in the proximity of nuclear facilities found that the majority of studies reported elevated rates [91]. This meta-analysis confirmed an increased risk of childhood leukemia near nuclear facilities with the highest contribution of excess cases and deaths from children aged < 10 years and living within 15 km from the nuclear site.

A few studies using cytogenetic methods have been conducted in Europe with children living close to nuclear plants or downstream of rivers from which water is used for cooling of reactors [90, 92]. Between 1988 and 1995 *in vitro* chromosome aberration assays were performed with peripheral lymphocytes from 5 healthy siblings of the leukemia cases and in 10 control children from the Elbmarsch Municipality [93 ??], 42 children from the Elbmarsch Municipality and 30 children from a control region [92], and 25 adults including 7 parents of children diagnosed with leukemia and 14 inhabitants near the Krummel nuclear plant and in 25 healthy adults (control subjects) living in the city of Bremen about 100 km southwest of Hamburg [94]. While two studies [93, 94] reported a significant fourfold higher rate of dicentric and/or ring chromosomes in peripheral blood lymphocytes in subjects leaving near the plant compared to control subjects, one study [92] failed to detect any such difference between exposed and control children.

Nuclear weapons fallouts, and nuclear accidents

During the period 1948-1967 three nuclear accidents took place in the Soviet nuclear weapon industry known as «Mayak Complex» established on the Techa River near Chelyabinsk, in the Southern Urals. During this period beta/gamma radioisotopes were released into the Techa River.

401 Several studies have been conducted on the population of 280,000 dwellings living in the area [95].
402 It has been estimated that about 8% of this population (124,000 people) were exposed to radioactive
403 isotopes such as ^{137}Cs, ^{106}Ru, ^{95}Zr, ^{89}Sr, ^{90}Sr, and that these received total accumulated doses above
404 1.0 Sv [96]. The increased frequency of CA that was observed in exposed children from this area
405 (0.56±0.08) compared to referents (0.29±0.07), resulting in an MR= 1.93 (Table 1), was
406 accompanied by a 1.7-fold increase in minisatellite mutation rate in the germline of exposed fathers
407 than in referents from rural areas (data not included in Table 1) [97]. Contrary to Hiroshima,
408 Nagasaki, and Chernobyl, the general population was exposed to short-lived radionuclides through
409 food, water and air in the period 1949-1963 due to the nuclear tests at the Semipalatinsk,
410 Kazakhstan (former Soviet Union), just south of the Altai region of Siberia. An impact of radiation
411 exposure during childhood was suggested by studies of adults living in this region. The area was
412 contaminated from 450 nuclear tests until 1989 of which 100 were atmospheric [98,99]. Cytogenetic
413 analysis of two or three generations within a family showed a presence of dicentric and ring
414 chromosomes in children born after the nuclear tests had ceased, suggesting family genomic
415 instability [100]. At the time of atmospheric bomb tests in 1949, about 25,000 people received doses
416 between 10 mSv and 1,500 mSv [96]. Studies of this population detected germ line mutations in
417 adults born between 1926 and 1960 and exposed to nuclear fall-out between 1949 and 1956, during
418 their childhood [101, 102].
419 There are special living conditions in Western Siberia where, in a large geographical area, mines,
420 chemical and nuclear industries are located. A follow-up study of 289 children [103] showed
421 significant deviations (including multi-aberrant cells) even in the “referent” population. Indeed,
422 because of the level of radiation pollution in this region, no unexposed children could be included in
423 the study and children in the lowest exposure group were used as referents [103, 104]. Despite the
424 acknowledged exposure misclassification, increased CA levels were reported for children exposed
425 to 0.6 cSv compared to those exposed to 0.05 cSv (3.94±0.44 and 2.58±0.59, respectively;
426 MR=1.53 Table 1).

The nuclear test site Syevernaya (in the period between 1955 and 1962, about 80 nuclear bomb tests were performed here) is located in Nóvaya Zemlyá, an area of Russia in which the population of the Tundra Nenets population lives. In this population increased cancer morbidity was detected (100). Similar to the children population in the Altai region, 20 years after cessation of nuclear tests, unstable chromosome aberrations such as rings and dicentrics were still detected in newborns [105]. An increased MN frequency (MR=1.4 and MR=1.6 in probably exposed and directly exposed children compared to referents) was detected in accidentally exposed children in the Goiania, Brazil radiological accident (Table 2); detected values are within the control values of other studies presented in Table 1 [106].

Contaminated building materials

In the period between 1982 and 1984 in Taiwan a number of buildings were constructed using reinforced steel contaminated by ^{60}Co which had been illegally discarded. The buildings were residential, schools and kindergartens, and it was estimated that 20% of 897 families were exposed to radiation doses higher then 5 mSv/year (in addition to background radiation). Several studies were carried out to estimate the radiation-induced genome damage simultaneously with physical dosimetry [108, 109, 110]. Although 1,500 subjects aged between 0 and 19 years were studied, findings for children were not reported separately [109], with the exception of a small study without a referent population in which the first blood sampling showed a significantly increased CA frequency (20.6±3.9%) in comparison with a second sampling conducted after evacuation from the contaminated buildings (8.7±1.5%), resulting in an MR=2.4 (Table 1). The issue of contaminated steel or other metals is not limited to the Taiwan episode: several reports [111, 112, 113] have addressed unsolved problems concerning building materials used in construction.

Conclusions

In general, genome damage caused by accidental overexposure to ionizing radiation may result from interactions such as the formation of DNA damage directly or via free radicals, but also from

damage to the nuclear membrane, lipid peroxidation, methylation disturbances, activation of a chain of signal molecules influencing the expression of apoptosis, and other mechanisms including hormonal, age related bioaccumulation of radionuclides, metabolism and clearance. Other contributing factors such as stress, malnutrition and infections may play major roles. At present, such conditions are predominantly found in some specific social environments in Ukraine and Belarus, but they could easily be envisaged in other parts of the world in conjunction with a nuclear accident. With respect to the genome damage discussed in this review, the main body of available data for children exposed to radiation comes from studies that were performed in Russia. Territories of the ex-Soviet Countries, as well as some other areas of our planet are still polluted as a consequence of nuclear tests and the nuclear industry. The resulting nuclear waste may lead to radiation exposure and complex exposures to radiation and chemical pollution, as is the case in a rocket test area or in spacedroms [114].

The studies considered in this systematic review consistently reported an increased frequency of CA and micronuclei in radiation exposed children compared to referents. Elevated CA levels were observed also in children exposed to high levels of radiation when compared to those exposed to lower levels [47,54,49,103]; this interpretation should be made despite the potential exposure misclassification of referent children for whom radiation exposure levels are hardly ever reported. Such a differential misclassification of exposure is expected to result in study findings that are toward the study null hypothesis (i.e., that there is no effect of environmental radiation exposure on genome damage in children) resulting in underestimated measures effect (MR).

The impact of internal contamination was indicated by a presence of rogue cells and by the higher frequency of dicentrics in exposed than in referent children as reported by several studies.

Beside a threat of accidental overexposures children are exposed routinely to ionizing radiation for diagnostic purposes which doses should be recorded and summarised as a cumulative life long dose. An increased risk of childhood leukaemia was detected in children who reported two or more postnatal X-rays [115]. The environmental burden during childhood could have a significant

influence on the adaptive capacity in adulthood and could be partly responsible for inter-individual differences in chemo- and radiosensitivity [116]. Additional radiosensitivity time windows should be investigated which may exist during childhood, e.g. in newborns and teens.

Populations suffering from radiological accidents, living in contaminated areas or ex-nuclear testing sites or close to radiochemical industries, are today subjected to an improved identification and monitoring, taking place in several medical centres. These groups of people constitute a large cohort including thousands of subjects and sometimes families with several generations. Local research centres often have stored biological samples, data on exposure and questionnaire data representing a valuable source of information that could be used for studying the delayed adverse effects of radiation on children and the transgenerational transfer of genome damage [96]. Integration and utilisation of such sources represent a great challenge and will probably be important in future studies of the consequences of children's exposure to ionizing radiation.

In Europe there is a dramatic discrepancy between the number of existing nuclear plants and the number of field studies on the potentially associated health consequences [117]. Regarding natural sources of radiation, consumers should be informed about possible health risks associated with the consumption of bottled mineral waters available on the market [6], in cases where increased radiation exposure may be significant. As only 5%-15% of childhood cancers seems to be related with familial and genetic factors [118]. the age related sensitivity should be subject to a closer study in order to avoid, at least, exposure of children during their most susceptible age periods. Similarly, governments should support reconstruction of dwellings in order to decrease radiation levels in homes and public buildings where children spend most of their time. Strict control of building materials for radio contamination should be performed (such as fly ash and steel). Genotoxicological studies of children living in the proximity of nuclear plants should be set as a priority in research programmes. At the same time there is a need for an arising preparedness of medical staff in case of nuclear accidents.

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Table 1. Chromosome aberration frequencies (mean ± SE), measured in children exposed to ionizing radiation and in referents, by type and level of exposure. The exposure level, sample size, age of the study groups (range), and the median ratio (MR) are reported for each study. Gaps excluded.

Type of exposure	Level of exposure[a]	Group: Sample Size	Age [b]	Mean ± SE (%)	MR	Details	Reference
^{137}Cs	18-55 x10^{10} Bq/km^2	Exposed: 103	6-15	2.74±0.1	**3.22**		42 Yeliseeva et al.,1994
Chernobyl	0.37-0.74 x10^{10} Bq/km^2	Exposed: 27		1.68±0,2	**1.98**		
	--	Referent: 16		0.85±0.1	**1**		
Radionuclides	74-148 Ci/km^2	Exposed: 11	4-11	4.0±0.3	**1.53**	Repeated measurements	43 Bochkov et al.,1991
Chernobyl	--	Referents: 13	4-11	2.6±0.2	**1**		
Radionuclides	148 x10^{10}Bq/km^2	Exposed: 24	10-12	0.62±0.08	**1.87**		46 Padovani et al.,1997
Chernobyl	--	Referent: 11	10-12	0.33±0.08	**1**		
Radionuclides	40 x10^{10}Bq/km^2	Exposed: 24	8-10	2.4	**4.00**	^{137}Cs whole-body counter	45 Padovani et al.,1993
Chernobyl	--	Referent: 10	8-10	0.6	**1**		
^{137}Cs	2.43 Bq/day	Exposed: 17	9-14	1.46±na	**1.02**	Belarus children	44 Barale et al.,1998
Chernobyl	--	Referents: 35	12-16	1.42±na	**1**	Italian healthy children	
		Exposed: 17	9-14	1.3±na	**3.25**	‰ Dicentrics	
		Referents: 35	12-16	0.4±na	**1**	‰ Dicentrics	
Radionuclides	--	Exposed: 49	1-16	2.5±0.1	**1.38**	Evaquated children	47 Vorobtsova al.,1995
Chernobyl	--	Exposed: 35	1-6	2.8±0.2	**1.55**	Liquidators'children	
	--	Referent: 25	3-16	1.8±0,2	**1**		
Radionuclides	0-6 cSv/y	Exposed: 25	6-15	3.93±0.2	**2.25**	Dicentrics = 0.44%	48 Pilinskaya et al.,1992
Chernobyl	0.8 cSv/y	Exposed: 25	6-15	3.78±0.3	**2.17**		
	--	Exposed: 25	6-15	2.62±0.2	**1.50**		
	--	Referent:25	6-15	1.74±0.2	**1**	Dicentrics = 0.02%	

Table 1 (cont.). Chromosome aberration frequencies (mean ± SE), measured in children exposed to ionizing radiation and in referents, by type and level of exposure. The exposure level, sample size, average age of the study groups, and the median ratio (MR) are reported for each study.

Type of exposure	Level of exposure [a]	Group: Sample Size	Age [b]	Mean±SE (%)	MR	Details	Reference
Radionuclides	--	Exposed: 15	2-5	2.38±1.9	**1.64**	Fathers with 1st - 2nd degree burns	51 Stepa. 1993
Chernobyl	--	Referents: 50	2-5	1.45±0.2	**1**		
Radionuclides	2.0-2.5 cSv	Exposed: 14	15	1.12±0.37	**1.90**	Exposed in utero	50 Suskov,2001
Chernobyl	1.5-2.5 cSv	Exposed: 18	10-14	1.24±0.4	**2.10**	Born 1987-1991	
cumulative dose	1.0-1.5 cSv	Exposed: 20	3-7	1.0±0.2	**1.69**	Born 1994-1998	
	--	Referent: 15	15-19	0.59±0.3	**1**	Born before 1986	
Radionuclides	10-376 mSv	Exposed: 22	15	9.07±1.34	**3.67**	Exposed in utero evaquated	67 Stepa.,2002
Chernobyl	19-52 mSv	Exposed: 20	15	7.63±2.92	**3.08**	Exposed in utero and after birth	
	--	Referent: 15	15	2.47±0.4	**1**	Living in unpolluted areas	
^{137}Cs, ^{90}Sr	35.9 kBq/m^2	Exposed: 20	6-10	1.17± na	**1.75**	% Dicentrics	71 Mikhalevich ,2000,
Chernobyl	2.22 kBq/m^2	Referents: 10	11-15	0.67± na	**1**	% Dicentrics	
Nuclear industry	> 1 Sv	Exposed: 15	9-11	0.56±0.08	**1.93**	Exposed to long-lived radionuclides	82 Testa,1998
Southern Urals	--	Referent: 11	9-11	0.29±0.07	**1**		
		Exposed: 15	9-11	0.07±0.03	**1.4**	% dicentrics	
		Referent: 11	9-11	0.05±0.02	**1**	% dicentrics	
Nuclear Industry	0.6 cSv	Exposed: 289	12-17	3.94±0.44	**1.53**	children with higher exposure	90 Druz.,1997
Western Siberia	0.05 cSv	Referent: 12	12-17	2.58±0.59	**1**	children with the lowest exposure	
Nuclear power plant	--	Exposed: 42	9-17	0.43 (0.24,0.7)[c]	**0.61**	‰ Dicentrics+ring chromosomes	81Bruske-Hoh, 2001
Elbmarsch, Germany	--	Referent: 30	9-17	0.706 (0.4,0.1)[c]	**1**	‰ Dicentrics+ring chromosomes	
^{60}Co (steel rebar)	5 mSv/y	Exposed: 18	4-18	20.6±3.9	**2.4**	1st phlebotomy	97 Hsieh ,2002
Taiwan, residential	5 mSv/y	Exposed:18	4-18	8.7±1.5	**1**	2nd phlebotomy, after evacuation	
Ra (indoor)	>1000 Bq/m^3	Exposed: 85	8-12	2.03±3.9	**1.69**	Schools' level	35 Bilban et al.,2001
Slovenia	<400 Bq/m^3	Referents: 20	8-12	1.2±0.59	**1**	Schools' level	
		Exposed: 85	8-12	0.08±0.44	**--**	% dicentrics	
		Referents: 20	8-12	0	**1**	% dicentrics	

[a]) -- = exposure levels not reported; [b]) range in years; [c]) 95% confidence interval; SE = standard error; na = not available

Table 2. In vitro (binucleated and mononucleated lymphocytes) and in vivo (reticulocytes) micronucleus assay data) measured in children exposed to ionizing radiation and in referents, by type and level of exposure. The exposure level, sample size, average age of the study groups, and the median ratio (MR) are reported for each study.

Type of exposure	Level of exposure[a]	Group : Sample Size	Age [b]	Mean ± SE (%)	MR	Comments	Reference
Ra (indoor)	>1000 Bq/m^3	Exposed: 85	8-12	6.5±2.5	**1.44**	Schools' level	35 Bilban et al.,2001
Slovenia	<400 Bq/m^3	Referenst: 20	8-12	4.5±1.9	**1**	Schools' level	
^{137}Cs	--	Exposed: 24	1-18	1.16±na	**1.6**	Directly exposed	95 da Cruz et al., 94
Accidental, Brazil	--	Exposed: 14	1-18	1.00±na	**1.4**	Probably exposed	
	--	Referents: 30	1-18	0.73	**1**		
Radionuclides							
Chernobyl							
^{137}Cs	35.9 kBq/m^2	Exposed: 20	10-17	0.75±0.08	**0.83**	binucleated lymphocytes	71 Mikhalevich ,2000
^{90}Sr	2.22 kBq/m^2	Referents: 10	10-15	0.90±0.08	**1**	binucleated lymphocytes	
^{137}Cs	35.9 kBq/m^2	Exposed: 20	10-17	2.71±0.27 [a]	**2.48**	mononucleated lymphocytes	71 Mikhalevich ,2000
^{90}Sr	2.22 kBq/m^2	Referents: 10	10-15	1.09±0.16 [a]	**1**	mononucleated lymphocytes	
Radionuclides	2.43 Bq/day	Exposed: 26	9-14	3.61±2.6	**1.80**	Belarus children	73 Zotti-Martelli.,99
Chernobyl	--	Referents: 30	12-16	2.0±2.1	**1**	Italian healthy children	
Radionuclides	0-20.2 Bq/kg	Exposed: 25	8-9	0.46±0.3	**0.90**	USA immigrants	72 Livingston et al,97
Chernobyl	--	Referents: 31	4	0.51±0.2	**1**		
Radionuclides	5-40 Ci/km^2	Exposed: 58	7-13	2.3 ±0.1	**2.3**		63 Pelevina et al.,96
Chernobyl	--	Referents: 136	8-13	1.0±0.06	**1**		
Radionuclides	--	Exposed: 54	6-16	0.19±na [c]	**15.8**	Evacuated children	70 Fedoretsova et.,97
Chernobyl	--	Referent: 94	6-16	0.012±na [c]	**1**		

-- = exposure levels not reported ; [a]) mononucleated lymphocytes; [b]) range in years; [c]) in vivo micronucleous assay; na, not available.

Table 3. Comet assay, FISH, and SCE results from measurements in children exposed to ionizing radiation and in referents, by type and level of exposure. The exposure level, sample size, the age range, and the median ratio (MR) are reported for each study.

Type of exposure	Level of exposure[a]	Group: Sample Size	Age	Mean±SE	Unit	MR	Details	Reference
				COMET	**DNA migration, µm**			
Radionuclides	$24x10^{10}$ Bq/km2	Exposed: 16	8-16	26.34±9.55		**0.62**	10 years after explosion	59 Frenzilli .,2001
Chernobyl	--	Referents: 39		16.46±4.6		**1**		
				FISH	**%**			
Radionuclides	--	Exposed: 11	8-19	0.65±0.1		**4.64**		69 Vorobtsova,2000
Chernobyl	--	Referents: 14	3-19	0.14±0.05		**1**		
				SCE	**%**			
Radionuclides	2.43 Bq/day	Exposed: 15	9-13	6.0±1.12		**0.85**	Belarus children	44 Barale et al.,1998
Chernobyl	--	Referents: 32	12-14	7.0±1.24		**1**	Italian healthy children	

[a]) -- = exposure levels not reported

Table 4. Correlation of detected break points (Stepanova 2002) and related disease in intrauterine exposed children.

LOCALIZATION OF BREAK SITES	RELATED DISEASE	LOCALIZATION OF BREAK SITES	RELATED DISEASE
1p35	NB, PV	5q33	ATL, LI, AML, MDS
1p13	AML-M7, PV	5q35	NHL, AML, MDS
1q32	NHL/CLD, MPD	7p15	AML, MPD
1q42	NHL/CLD, MPD	7q33	ALL, AML, CLD, MDS, NHL, PV
2q33	CLL	9q34	ALL, AML, CML, MDS, MPD, NHL
3p21	PA, AC salivary gland, AC/SCC, lung, CLD, NHL, AC kidney	13q32	LI, ALL, MDS, MPD
3q25	AML, MDS, AC kidney	17q21	AML, breast cancer
5p15	ATL, AML	17q25	AML
5p13	ATL	22q13	AML-M7, ALL, MN
5q31	ALL, AML, MDS		

*** AC Adenocarcinoma, ALL Acute lymphoblastic leukemia, AML Acute myeloid leukemia, subclasified FAB M1 trough M7, ATL Adult T-cell leukemia/lymphoma, CLD Chronic lymphoproliferative disorder, CLL Chronic lymphocytic leukemia, LI Lipoma, MDS Myelodysplastic syndrome, MPD Myeloproliferative disorder, NB Neuroblastoma, NHL Non-Hodgkin´s lymphoma, subclassified B or T cell lineage, PA Pleomorphic adenoma, PV Polycythemia vera, SCC Small cell carcinoma.