Središnja medicinska knjižnica

1 **Genomic damage in children accidentally exposed to ionizing radiation: a review of the**

2 **literature.**

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24 **Layout**

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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.

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 < 0·0001) 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].

171   As radon daughter products follow the metabolic pathway of calcium, its incorporation into

172   children's skeleton poses a significant health risk [28]. Due to age dependent developmental stage

173   of the gastrointestinal system of children, the highest absorption of radon is in newborns and in

174   children between 13 and 17 years of age [27,29]. This is accompanied with high water intake in

175   newborns and children in comparison with adults [30]. Children and adolescents are target

176   populations for intake of water which can be radiocontaminated, due to the increased usage of

177   bottled water in Europe and its use for production of a number of different drinks favoured by the

178   youngest. The increased effective dose from radiocontaminated mineral water may be up to seven

179   times higher in infants and teens than the maximum level recommended by the World Health

180   Organization (100 μSv,) [31]. It has been suggested that this exposure may be specifically relevant

181   for the hormonal activity of testosterone and oestrogen during puberty when final maturation of

182   skeleton occurs [32]. Non breast fed infants less than 1 year of age may receive doses up to 0.28

183   mSv/y if their diet is exclusively prepared with mineral water with elevated radon concentrations

184   from ^{226}Ra decay [33]. In addition, such waters contain other radionuclides such as ^{210}Pb and ^{222}Ra

185   also contributing to the total received dose [33].

186   The health risk related to indoor radon exposure is still a subject of discussion. It has been shown

187   that residential radon exposure may contribute to increased cancer incidence. The average radon

188   exposure of 50 Bqm^{-3} has been estimated to be responsible for 13-25% of myeloid leukaemia cases

189   at all ages [34,35]. Indoor exposure at an annual dose of 7-11 mSv from radon has been reported to

190   be associated with a significantly increased frequency of chromosome aberrations (MR=1.69, Table

191   1) and micronuclei (MR=1.44, Table 2) in children [36]. To decrease radon levels in the working

192   and living environment some countries have established programmes for remediation work in

193   buildings, primarily schools and homes [37].

194

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

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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.

247   *In utero exposure*. The Chernobyl accident affected also pregnant women who were exposed to

248   different levels of radiation before being evacuated. A study using G banding was performed on two

249   groups of children exposed *in utero* and during childhood to ionizing radiation [56]. Children born

250   by mothers who were pregnant at the time of the accident and evacuated shortly afterwards were

251   exposed to radiation levels ranging between 10 and 376 mSv while children exposed *in utero* and

252   chronically during the childhood experienced a cumulative dose of 19-52 mSv. An increased

253   frequency of CA was detected in newborns from both groups of women. As shown in Table 1 mean

254   frequencies of 9.07% ±1.34 and 7.63%±2.92 of CA were measured in the group of intrauterine

255   exposed children and in children exposed *in utero* and after birth, respectively, compared to a

256   frequency of 2.47%±0.4 detected in referent children (MR= 3.67 and 3.08). Translocations,

257   inversions and deletions represented almost 80% and 70% of chromosome type aberrations in

258   intrauterine exposed and continuously exposed children, respectively [56]. Non random distribution

259   of chromosome damage was detected: the most frequently involved chromosomes were

260   chromosome 1, 3, 5, 7, 9, 11, 13, 21 and 22 [56]. On the background of the available scientific

261   evidence, this predominant localization of break points correlates with diagnostics markers of

262   neoplastic disease as summarized in Table 4 [57]. All detected bands at which chromosome

263   breakage was present are non-random and related with the described neoplasias.

264   *Parental exposure*. A high frequency of aberrant cells (1.12± 0.37%) was measured in children

265   exposed *in utero* to 2.0-2.5 cSv, in those born between 1987-1991 (1.24±0.4) as well as in children

266   born between 1994-1998 (1±0.2) compared to children born before the Chernobyl accident (0.59±

267   0.3%), with MRs of 1.90, 2.1, and 1.69, respectively [58].A long-term follow-up study of

268   populations living in a contaminated area of 15, Ci/km^2 [58] showed increased genome damage in

269   children of irradiated parents (Table 1). The highest frequency of aberrant cells (1.24± 0.4%) was

270   measured in children born by mothers who were continuously exposed to ionizing radiation

271   following the Chernobyl accident (MR=2.1).

272   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

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299 compared to referent children while another [65] detected similar levels of micronuclei in exposed

300 and referents (Table 2). Using the *in vivo* micronucleus assay, liquidators from Chernobyl and their

301 children evacuated following the nuclear accident [66] were observed to express significantly

302 increased mean micronuclei levels in peripheral lymphocytes compared to referent children (0.19‰

303 and 0.012‰ micronucleated cells, respectively, MR=15.8). This is the only available study on a

304 population environmentally exposed to radiation monitored by the *in vivo* MN assay.

305 The Comet assay has been used to estimate genome damage levels in children from Belarus 10

306 years after the Chernobyl accident [67]. An increased genome damage was still present in their

307 lymphocytes (Table 3), a finding that could be explained as a "clastogenic factor" present in 19% of

308 these children [67]. When the translocation frequency was measured using FISH (Table 3) in a

309 group of exposed children and in age matched referents, higher levels of translocation were found in

310 the former (0.65%±0.1) than in the latter group (0.14%±0.05) corresponding to an MR of 4.64 [68].

311 In the same study higher MN frequencies were found in exposed children than in exposed adults

312 (0.06‰), a finding that is suggestive of a higher sensitivity of children to ionising radiation induced

313 cytogenetic damage, since it seems unlikely that the children were exposed to higher levels of

314 radiation than their parents.

315 **Antioxidants and lipid peroxidation.**

316 Several studies (not included in any table) have investigated the association between radiation

317 exposure, lipid peroxidation disorders, and cytogenetic damage. Analyses of children born by

318 mothers who were exposed to low doses of radiation before pregnancy showed that in regions

319 contaminated by radionuclides, these children suffered from lipoperoxidase disorders and that the

320 levels of essential antioxidants such as vitamin A and E were low. For mothers on a diet

321 supplemented with these vitamins during pregnancy, the chromosome aberration frequency in their

322 newborns was significantly lower in comparison with children born by mothers without such

323 vitamin supplemented diet [69]. The complexity of interaction between the organism in

324 development and radiation is also illustrated by a bimodal pattern of distribution of the gluthatione

325 system [70, 71] in children born by mothers exposed to different dose levels. In children born by

326 mothers exposed to doses between 0.8 and 30 cSv, increased levels of reduced plasma glutathione

327 (up to 90 µM) could be detected, while in mothers exposed to doses between 30 cSv and 60 cSv,

328 severe decrease (5 µM) was detected. Gluthatione mediates a reduction of at least two vitamins,

329 alfa-tocopherol and ascorbic acid which are critical in prevention of lipid peroxidation. Additional

330 consequences of exposure to ionizing radiation and disturbances of glutathione level are seen in

331 cases of combined radiochemical exposure. Increased levels of polycyclic aromatic carbons (PAH)-

332 DNA adducts are found in human placenta of mothers exposed to both ionizing radiation and

333 environmental PAH, suggesting a possibly higher health risk for the foetus in a case of complex

334 exposure than would be expected exclusively from PAH concentrations in air [72].

335 **Radiation induced adaptive response.**

336 An adaptive response of subjects exposed to low doses of chemical agents or radiation has

337 frequently been investigated by Russian and Ukrainian scientists. The existence of radiation

338 associated hormesis (i.e. the concept that small doses of radiation may reduce the damage to levels

339 even lower than those observed in unexposed controls) is still debated in the literature. The adaptive

340 response is a characteristic feature of both mammalian and plant cells in their response to various

341 mutagenic agents [73]. This phenomenon occurs when cells are treated with a low dose of a

342 clastogen; such a pre-treatment may then reduce the effect of a subsequent treatment with a higher

343 dose of the same or a similar agent (the challenging treatment). Adaptation can be measured by the

344 challenge assay in which lymphocytes isolated from exposed and control subjects are treated with

345 either 1 Gy or a combination of 0.05 Gy and 1 Gy. Compared to children living in Moscow's urban

346 polluted areas, increased micronuclei frequencies were reported among children from the Chernobyl

347 area exposed to radiation by living in areas with contamination levels ranging between 5 and 40

348 Ci/km^2. Lymphocytes of children from these radiocontaminated areas showed increased frequencies

349 of chromosome aberrations and micronuclei in the challenge assay, suggesting that, in this exposed

350 population, subjects express a radiosensitivity with no indication of an adaptive response. These

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351 results may show that a routine application of chromosome aberration and/or micronucleus assay

352 without also employing a challenge assay may not be sufficient for the detection of genomic

353 instability [63]. By comparing this radiosensitivity with the observations of adaptive response in the

354 adult and children populations from Ural (internal exposure with ^{90}Sr from the Techa River) and the

355 Chernobyl regions, some common features were apparent. In both groups of exposed children,

356 individuals with high radiosensitivity were recognized after a challenging dose of 1 Gy and using

357 MN as the endpoint. Among referent children from the Moscow region, inter-individual differences

358 in MN frequencies were significantly lower after challenge assay than in exposed group. Based on

359 such sada It is suggested that adaptive response is not developed and will not be expressed in

360 adulthood if a person is exposed as a child to elevated levels of radiation or other xenobiotics [74,

361 75].

362 **Hiroshima and Nagasaki**

363 The Chernobyl disaster resulted primarily in radiation via internal contamination, whereas after the

364 Hiroshima and Nagasaki bombings the primary source was gamma radiation and fast neutrons. This

365 represents different types of exposures, which are also associated with different cancer incidence

366 distributions [76]. Two to three years after the bombing, leukemia was the first cancer to be linked

367 with exposure with the highest incidence of leukemia detected in people exposed during their

368 childhood [77]. Besides the increase in leukemia, elevated rates of solid cancers such as cancers of

369 the breast, lung, and colon have been reported which seem to be larger among subjects exposed

370 during their childhood than among those exposed as adults [78].

371 Cytogenetic analyses of exposed populations started 15 years after the bombing [79] due to the fact

372 that cytogenetic methods were not introduced until the 60's. A number of different research teams

373 have been involved in studying health consequences in survivors and studies are still on going

374 among children of exposed subjects. [80]

14

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].

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.

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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).

427 The nuclear test site Syevernaya (in the period between 1955 and 1962, about 80 nuclear bomb tests

428 were performed here) is located in Nóvaya Zemlyá, an area of Russia in which the population of the

429 Tundra Nenets population lives. In this population increased cancer morbidity was detected (100).

430 Similar to the children population in the Altai region, 20 years after cessation of nuclear tests,

431 unstable chromosome aberrations such as rings and dicentrics were still detected in newborns [105].

432 An increased MN frequency (MR=1.4 and MR=1.6 in probably exposed and directly exposed

433 children compared to referents) was detected in accidentally exposed children in the Goiania, Brazil

434 radiological accident (Table 2); detected values are within the control values of other studies

435 presented in Table 1 [106].

436 **Contaminated building materials**

437 In the period between 1982 and 1984 in Taiwan a number of buildings were constructed using

438 reinforced steel contaminated by ^{60}Co which had been illegally discarded. The buildings were

439 residential, schools and kindergartens, and it was estimated that 20% of 897 families were exposed

440 to radiation doses higher then 5 mSv/year (in addition to background radiation). Several studies

441 were carried out to estimate the radiation-induced genome damage simultaneously with physical

442 dosimetry [108, 109, 110]. Although 1,500 subjects aged between 0 and 19 years were studied,

443 findings for children were not reported separately [109], with the exception of a small study without

444 a referent population in which the first blood sampling showed a significantly increased CA

445 frequency (20.6±3.9%) in comparison with a second sampling conducted after evacuation from the

446 contaminated buildings (8.7±1.5%), resulting in an MR=2.4 (Table 1). The issue of contaminated

447 steel or other metals is not limited to the Taiwan episode: several reports [111, 112, 113] have

448 addressed unsolved problems concerning building materials used in construction.

449

450 **Conclusions**

451 In general, genome damage caused by accidental overexposure to ionizing radiation may result

452 from interactions such as the formation of DNA damage directly or via free radicals, but also from

17

453 damage to the nuclear membrane, lipid peroxidation, methylation disturbances, activation of a chain

454 of signal molecules influencing the expression of apoptosis, and other mechanisms including

455 hormonal, age related bioaccumulation of radionuclides, metabolism and clearance. Other

456 contributing factors such as stress, malnutrition and infections may play major roles. At present,

457 such conditions are predominantly found in some specific social environments in Ukraine and

458 Belarus, but they could easily be envisaged in other parts of the world in conjunction with a nuclear

459 accident. With respect to the genome damage discussed in this review, the main body of available

460 data for children exposed to radiation comes from studies that were performed in Russia. Territories

461 of the ex-Soviet Countries, as well as some other areas of our planet are still polluted as a

462 consequence of nuclear tests and the nuclear industry. The resulting nuclear waste may lead to

463 radiation exposure and complex exposures to radiation and chemical pollution, as is the case in a

464 rocket test area or in spacedroms [114].

465 The studies considered in this systematic review consistently reported an increased frequency of CA

466 and micronuclei in radiation exposed children compared to referents. Elevated CA levels were

467 observed also in children exposed to high levels of radiation when compared to those exposed to

468 lower levels [47,54,49,103]; this interpretation should be made despite the potential exposure

469 misclassification of referent children for whom radiation exposure levels are hardly ever reported.

470 Such a differential misclassification of exposure is expected to result in study findings that are

471 toward the study null hypothesis (i.e., that there is no effect of environmental radiation exposure on

472 genome damage in children) resulting in underestimated measures effect (MR).

473 The impact of internal contamination was indicated by a presence of rogue cells and by the higher

474 frequency of dicentrics in exposed than in referent children as reported by several studies.

475 Beside a threat of accidental overexposures children are exposed routinely to ionizing radiation for

476 diagnostic purposes which doses should be recorded and summarised as a cumulative life long dose.

477 An increased risk of childhood leukaemia was detected in children who reported two or more

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

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	24×10^{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.