What strategy of secondary prevention after a nuclear beyond design-basis accident?

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Introduction

There is no doubt, that ionizing radiation causes solid cancers and other malignancies such as lymphomas and various forms of leukaemias. Malformations (due to teratogenesis or mutations), other genetic abnormalities or even more severe genetic abnormalities in the following generations as well as disturbed brain development are also scientifically accepted consequences of ionizing radiation.

Confronted with these facts we must decide within the society which risks we will and can accept from radiation produced by normal and abnormal operation of nuclear power plants.

In the case of a nuclear accident like the beyond design-basis accident (an in german so called «SuperGau») of Chernobyl or the Fukushima - we must protect the population as far as possible and as much as technically achievable from the possible consequences of ionizing radiation.

We have learned lessons from the Chernobyl disaster and we can implement this lessons for reducing radiation damage in people affected by the Fukushima Dai-ichi accident.

We must take into consideration that ionizing radiation causes not only malignancies, teratogenesis and genetic disorders but also diseases of the endocrine system, the heart and the circulatory system, in addition to psychological problems and psychoses, stillbirths[1], increased perinatal mortality and disturbances of the sex odds ratio of lifebirths.[2]

Proposals for a secondary prevention strategy after a nuclear power plant disaster

In the eventual case of a nuclear disaster in Switzerland we would propose to our government:

- Distribution of stable iodine already when a release of radioactivity could just be anticipated or when a meltdown is possible.[3,4] After the Chernobyl accident a significant increase of thyroid cancer incidence in children and young adults was observed.[5] Iodine prophylaxis has been shown to be a safe and effective procedure among 10 millions of children in Poland, preventing ^{131}iodine induced thyroid cancers. ^{131}iodine has a short half live of 8 days. Eighty days after incorporation an individual dosimetry is no longer useful, because almost all incorporated ^{131}iodine has decayed.
    - If prophylactic intake of iodine tablets was not done, routine sonographic screening for thyroid cancer in children is mandatory.
- Food must be systematically measured for radioactive isotopes and limits must be set in a differentiated manner to protect with first priority children and, especially, pregnant women.
- Children[6] and adults as well, must be controlled by whole body counter measurements with best technical instruments to detect anticipated and unanticipated burdens of ^{137}cesium and ^{134}cesium.
- Sampling deciduous teeth of children to measure ^{90}strontium contamination of children.[7,8]
- Measures must be taken to reduce the burden of Isotopes such as providing immediately clean food. Intake of pectines aiming at depletion of the body burden of isotopes is strongly recommended[9,10]. Protection against extern radiation resulting from the contamination of the soils with radioisotopes is also important. Maybe the only realistic measure will be evacuation of contaminated regions.
- In Switzerland we as an NGO would never accept a dose limit of 20 mSv/year for children as a long-term dose limitation.

- As an indicator of detriments one have to build up cancer registries[11] long before the accident, as well as malformation registries and other morbidity registries. What happens with the incidence of malignant tumors, general morbidity of children and adults after a nuclear accident? We have to get facts - not epidemiological estimates as until now - about these consequences.
- For prevention of cardiac diseases children must undergo cardiac examination to find and define cardiac arrhythmias if they have a detectable ^{137}cesium- and ^{134}cesium burden.[12]
- Statistical research must be done to observe the sex odds ratio before and after the Fukushima accident.[2] The human embryo is very sensitive to radiation, female embryos more than males.
- Scientific research must take into consideration the genomic instability produced by radiation, which will be transmitted to the next generations. Perhaps we will have a paradigm change in radiation biology from target theorem to a more complicated model of radiation damages. An already accepted concept?[13]

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Reference 1

Articles

Stillbirths among offspring of male radiation workers at Sellafield nuclear reprocessing plant

Louise Parker, Mark S Pearce, Heather O Dickinson, Murray Aitkin, Alan W Craft

Summary

Background Ionising radiation is a known mutagen, but few studies have examined transgenerational effects of paternal exposure in human beings. The workforce at the Sellafield nuclear reprocessing plant in the county of Cumbria, UK, is the most highly exposed workforce in western Europe and North America. This study, which is part of a larger programme of work investigating the health of the children of the Sellafield workforce, set out to find whether there was evidence of an association between stillbirth risk and paternal exposure to ionising radiation.

Methods We collected details from birth registration documents for all singleton 248 097 livebirths and 3715 stillbirths in the county of Cumbria 1950–89. Within this cohort the 130 stillbirths and 9078 livebirths to partners of male radiation workers employed at Sellafield were identified. Logistic regression was used to analyse the relation between stillbirth risk and father's preconceptional radiation exposure, with adjustment for social class, year of birth, father's age, and birth order.

Findings A significant positive association was found between the risk of a baby being stillborn and the father's total exposure to external ionising radiation before conception (adjusted odds ratio per 100 mSv 1·24 [95% CI 1·04–1·45], p=0·009). The risk was higher for stillbirths with congenital anomaly and was highest for the nine stillbirths with neural-tube defects. The statistical models predicted that, were the association to be interpreted as causal, between 0 and 31·9 of the 130 stillbirths to the workforce may be attributable to father's radiation exposure.

Interpretation The findings of an increased risk of stillbirth with increasing paternal occupational exposure to external radiation are qualitatively consistent with those from animal models, though the risk estimate is higher. Although we cannot exclude the possibility of an unmeasured risk factor for stillbirth, confounded with paternal preconceptional irradiation, extensive checks confirmed that the statistical models were a good fit to the data and there was not statistical evidence of unmeasured factors.

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Introduction

There has been concern about possible transgenerational effects of exposure to ionising radiation since the earliest days of radiobiological research. Exposure of male mammals to preconceptional ionising radiation causes a range of adverse outcomes in their offspring, including death, cancer, and congenital anomaly.[1–5] In 1988 a UK government committee[6] investigating the excess risk of leukaemia in children in the vicinity of the Dounreay nuclear-fuel reprocessing plant in the north of Scotland recommended that "epidemiological studies should be set up to consider any possible effects on the health of the offspring of parents occupationally exposed to radiation". This concern received further emphasis in 1990 when Gardner and colleagues[7] reported the results of a case-control study of young people diagnosed with leukaemia and lymphoma in west Cumbria, UK, concluding that the substantial excess of these malignant disorders in young people in Sellafield could be the result of their fathers' preconceptional radiation exposure while employed at Sellafield, the adjacent nuclear-fuel reprocessing plant, with exposure during the period immediately before conception being particularly important. However, the hypothesis that paternal preconceptional irradiation is causally associated with childhood leukaemia and lymphoma has not been supported by further epidemiological investigations.[8–11]

Any transgenerational effects of paternal preconceptional irradiation would be likely to appear as outcomes such as congenital anomalies rather than childhood leukaemia since these have a much higher heritable component.[12] The Sellafield workforce is of particular interest because of its comparatively high exposures to ionising radiation.[13] The current programme of work set out to study transgenerational effects of paternal preconceptional irradiation in the offspring of this workforce, by investigating the association of such irradiation with the sex ratio and adverse health outcome in their children (stillbirth, infant death, cancer).[8,14–16] The present study investigated whether there was evidence of increasing risk of stillbirth (including those with congenital anomaly), within the cohort of children born to male radiation workers at the Sellafield site, with increasing external or internal preconceptional exposure to ionising radiation during either the 90 days immediately before conception (ie, during the period of spermatogenesis), or the entire preconceptional period of employment within the nuclear industry.

Methods

Participants

A cohort study was done of all singleton births from 1950 to 1989 to fathers employed at Sellafield while resident in the county of Cumbria. Preconceptional radiation doses were estimated from annual external dose summaries and from routine internal dose assessments. Doses in the 90 days before conception were estimated pro rata from annual dose summaries. Investigation of the relation between paternal preconceptional irradiation and stillbirth by specific cause was possible only from 1961 onwards. The effect of errors in 90-day dose estimates resulting from their derivation pro rata from annual dose estimates was assessed in a nested case-control study that used external doses constructed directly from monthly film-badge data and internal doses from special assessments. These were very time consuming to collate and would have taken several years to compile for the entire workforce.

Database—livebirths and stillbirths

The Cumbrian Births Database was constructed from birth registration details for all 248 097 singleton livebirths and 3715 stillbirths (babies born dead after at least 28 weeks of gestation) to mothers who lived in Cumbria in the period Jan 1, 1950, to Sept 30, 1989,[15,16] with exclusion of births for which no father was recorded on the birth registration (a further 8854 livebirths, 293 stillbirths). Multiple births were excluded because they may not be independent conceptions (5446 livebirths, 229 stillbirths). The fathers' occupations recorded at birth were social-class coded.[17] Parents' names were used to identify siblings, and their birth order was inferred from their date of birth.

Livebirths and stillbirths on the Cumbrian Births Database to fathers employed at the Sellafield site since 1947 were identified in a linkage procedure described in detail elsewhere.[15] The child-father linkage was done in several stages. First, a computer-matching exercise was done in which, for each male Sellafield employee, the birth register was searched for all entries where the father had an identical or similar-sounding (Soundex) surname, common forename initials, and was aged between 15 years and 60 years at the time of the birth. After comparisons of the information on the birth entry with that in the employee dossier—ie, full name of employee, address, full name and previous names of spouse, occupation, place of birth of employee (births after 1969 only)—each possible child on the database was then flagged as being definitely, definitely not, or possibly the offspring of a particular employee. Information from the entry of a child definitely or definitely not linked to an employee was used to assist with subsequent matching. Many of the matches regarded as possible were resolved by more detailed examination of the dossiers and by examination of electoral registers. The final step in the matching process was to search the database for children who were unlinked siblings of matched children.

A validation of the linkage process was done in which postal questionnaires were sent to 1835 past and present male Sellafield employees, 1244 of whom replied. Hence the error in matching was estimated to be 1·7% (0·3% of the children were matched but not reported on questionnaires and 1·4% were reported on questionnaires but not matched). The radiation-worker cohort comprised those children whose fathers had been exposed to ionising radiation during the course of their employment at Sellafield, before conception. The stillbirth linkage was done twice independently. One of the 130 stillbirths in the radiation-worker cohort was linked by use of father's forenames and surname only, all others were matched on father's forenames and surname and at least one other piece of information from the child's birth certificate. Births to radiation workers for whom social class was unavailable (13 livebirths, 0 stillbirths) were not included.

Cause of death was recorded on stillbirth registration from 1961 onwards and those to radiation workers were coded by means of the grouping of Alberman and colleagues.[18] Hence two mutually exclusive categories were identified: congenital anomaly (Alberman and colleagues' group 1) and all other causes. Within the first category specific causes were identified. Date of birth was available for Sellafield employees so the age of these fathers at the birth of their children was calculated. Details of the database showing the distribution of livebirths and stillbirths to

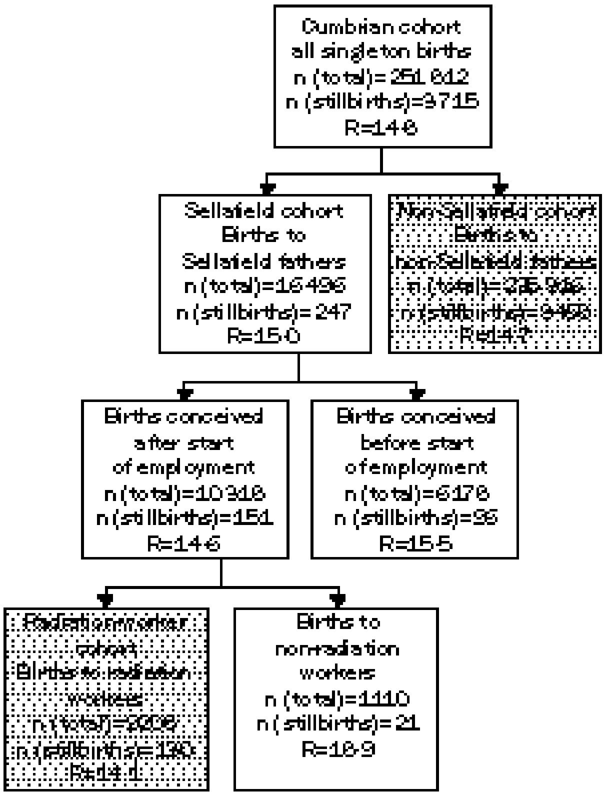


Figure 1: **Cumbrian births database—singleton births Jan 1, 1950 to Sept 30, 1989**

Excludes fathers not recorded and radiation workers with social class unknown. Tinted boxes show cohorts included in main analysis. R=stillbirth rate/1000 births.

the non-Sellafield cohort, the Sellafield workforce, and the radiation-worker cohort are shown in figure 1.

Length of gestation

To facilitate an accurate estimate of the time of conception, and thus paternal preconceptional irradiation, gestational age at birth was obtained from hospital records for 67 (52%) stillbirths to radiation workers (median 36 weeks measured from date of conception—ie, date of last menstrual period plus 14 days), whereas for the remainder gestational age at birth was assumed to be the median of that reported nationally for stillbirths (34 weeks).[19] Gestational age at birth was assumed to be 38 weeks for livebirths but was also obtained from hospital records for 273 (3%) of the livebirths (median 38 weeks).

Database—radiation dosimetry information

British Nuclear Fuels plc provided dosimetry data captured as part of the routine monitoring of the workforce for regulatory and radiological protection purposes.

Occupational exposures to external ionising radiation were monitored prospectively by film badges that were usually changed monthly. Each employee's film badge doses were summed over a calendar year to produce an annual summary dose (ASD). For any employee transferring to Sellafield from another site within the nuclear industry, the occupational dose accrued up to that time was included in the dose estimates. The accuracy of these doses has been reported.[20]

For the cohort analysis, two external ionising-radiation doses were estimated from ASD: ASD90 (the dose in the 90 days before conception, estimated pro rata from the ASD for that year, or from ASD for 2 consecutive years if the 90-day period spanned 2 calendar years, and ASDtotal (the total dose up to the time of conception with the dose for the year of conception estimated pro rata from the ASD for that year).

For the nested case-control study, two doses were calculated by summation of individual film-badge records: FB90 (the dose

	Livebirths	Stillbirths	Stillbirth rate per 1000 births	Odds ratio (95% CI)*
Decade				
1950–1959	65 028	1485	22·3	. .
1960–1969	67 745	1166	16·9	. .
1970–1979	51 816	539	10·3	. .
1980–1989	47 259	278	5·8	. .
Social class				
I	10 783	88	8·1	0·60 (0·48–0·74)
II	38 125	478	12·4	0·88 (0·79–0·97)
III, non-manual	19 806	228	11·4	0·74 (0·64–0·85)
III, manual	96 802	1489	15·1	1·00
IV	38 779	669	17·0	1·08 (0·98–1·18)
V	21 763	394	17·8	1·13 (1·01–1·26)
Other†	5790	122	20·6	1·14 (0·94–1·37)
Birth order				
1	124 384	2058	16·3	1·00
2	69 231	766	10·9	0·71 (0·65–0·77)
3 and 4	33 683	511	14·9	0·92 (0·83–1·02)
5 and over	4550	133	28·4	1·57 (1·31–1·89)
Total	231 848	3468	14·7	. .

*Adjusted for year of birth and the other covariate.
†Armed Forces, unemployed, and unknown social class.

Table 1: **Livebirths and stillbirths by decade, social class, and birth order (non-Sellafield cohort)**

in the 90 days before conception); FBtotal (the total preconceptional dose).

Urinalysis data were used to assess internal ionising-radiation exposure. The total preconceptional gonadal dose was estimated by methods based on International Committee on Radiological Protection (ICRP) models,[21] and the gonadal dose in the 90 days immediately before conception was calculated pro rata from the annual dose with the exception of tritium (biological half-life 10 days), which was calculated specifically for the 90-day preconceptional period. Where estimated gonadal doses were below 0·01 mSv (eg, uranium), or where doses were unavailable (eg, ruthenium), an uptake flag, indicating that the father had been exposed to this radionuclide, was used.

The statistical software packages Stata, version 6.0, and Glim, version 4, were used.

Cohort study

The relation between stillbirth risk and year of birth, sex, paternal social class, and birth order (all putative risk factors for stillbirth[22]) in the non-Sellafield cohort was modelled by logistic regression. The estimated effects of year of birth and of significant demographic variables were assumed to apply to the radiation-worker cohort.

Paternal age was not available for the non-Sellafield cohort because this information is held within the confidential particulars of the birth-registration document to which we did not have access. The only available data on paternal age and stillbirth risk are national data for 1973 onwards, aggregated over year of birth, social class, and birth order.[23] This dataset was used to estimate the relation between paternal age and stillbirth risk that was assumed to apply to the radiation-worker cohort.

Odds ratios are reported for trend with dose measured per 100 mSv for total paternal preconceptional irradiation and per 10 mSv for 90-day irradiation.

Significance was assessed by the likelihood-ratio-test statistic (LRTS). One-sided LRTS p values are presented for odds ratios with paternal preconceptional irradiation. 95% CI for odds ratio with dose were based on profile-likelihood estimation.

Further modelling of the risk of stillbirth in relation to paternal preconceptional irradiation was done to allow for the possible effects of unmeasured variables,[24] variation between fathers in the effect of paternal preconceptional irradiation,[25] and variation in risk of stillbirth between families.[25] The sensitivity of the model to external (offset) versus internal adjustment for covariates was also investigated.

As part of the checking process for the model, various alternative forms were considered for the dose-response relation.

	Radiation workers			Non-radiation workers		
	Livebirths	Stillbirths	Stillbirth rate per 1000 births	Livebirths	Stillbirths	Stillbirth rate per 1000 births
Decade						
1950–1959	1657	44	25·9	469	17	35·0
1960–1969	2838	52	18·0	263	4	15·0
1970–1979	1704	16	9·3	154	0	0
1980–1989	2879	18	6·2	203	0	0
Social class						
I	1528	14	9·1	94	1	10·5
II	999	14	13·8	118	3	24·8
III, non-manual	621	10	15·8	140	2	14·1
III, manual	3446	37	10·6	354	8	22·1
IV	2187	54	24·1	311	6	18·9
V	297	1	3·4	72	1	13·7
Birth order						
1	4079	67	16·2	619	14	22·1
2	3161	33	10·3	299	4	13·2
3 and 4	1618	27	16·4	141	2	14·0
5 and over	220	3	13·5	30	1	32·3
Paternal age (years)						
<20	36	1	27·0	30	1	32·3
20–30	5303	62	11·6	528	9	16·8
31–44	3571	61	16·8	489	10	20·0
⩾45	168	6	34·5	42	1	23·3
Total	9078	130	14·1	1089	21	18·9

Table 2: **Livebirths and stillbirths by decade, social class, and birth order and paternal age (Sellafield cohort)**

These ranged from log(dose)—giving less weight to high doses—to dose to the power of six, which gives greater weight to high doses. Threshold and broken-stick models were also considered.[26]

The goodness-of-fit of the final models was checked for the non-Sellafield cohort (Pearson χ^2 for categorical data) and the radiation-worker cohort (deciles of risk tests for continuous data). The model was also checked by using it to predict the number of stillbirths to the two groups of Sellafield fathers not otherwise included in this study—births conceived before the father started employment at Sellafield, and births to non-radiation workers at Sellafield (figure 1).

To investigate whether any specific births had undue influence on the final results, outliers (ie, livebirths and stillbirths with the highest paternal preconceptional irradiation) were removed. The number of stillbirths attributable to paternal preconceptional irradiation was estimated for each model.[27] In addition, odds ratios in relation to ASDtotal were calculated for each stillbirth cause category for the cohort from 1961 onwards.

	ASD90*		Median (range) ASDtotal† (mSv)
	Number of births	Median (range) ASD90 (mSv)	
Decade			
1950–1959	1451	2·6 (0·01–28)	22·0 (0·01–439)
1960–1969	2108	2·1 (0·02–16)	39·2 (0·07–911)
1970–1979	1254	2·0 (0·01–18)	31·0 (0·01–741)
1980–1989	2373	1·0 (0·01–33)	26·7 (0·01–646)
Social class			
I	1408	1·0 (0·01–22)	24·5 (0·03–552)
II	778	1·9 (0·02–33)	36·1 (0·04–412)
III, non-manual	412	0·4 (0·01–10)	15·2 (0·01–393)
III, manual	2660	1·8 (0·01–24)	30·4 (0·01–911)
IV	1779	3·3 (0·01–28)	40·1 (0·02–826)
V	149	1·5 (0·01–13)	15·2 (0·05–309)
Paternal age (years)			
<20	36	0·8 (0·05–6)	24·5 (0·11–21)
20–30	4349	1·8 (0·01–27)	25·6 (0·01–450)
31–44	2676	1·7 (0·01–33)	38·8 (0·01–911)
⩾45	125	2·0 (0·01–14)	48·7 (0·25–501)
Total	7186	1·7 (0·01–33)	30·1 (0·01–911)

*Births with ASD90=0 excluded. †For number of births, see table 2.

Table 3: **External preconceptional doses of ionising radiation (radiation-worker cohort)**

Radionuclide	Exposed livebirths		Exposed stillbirths		Odds ratio (95% CI)†
	Number of births	Median (range) dose (mSv)	Number of births	Median (range) dose (mSv)	
Plutonium	3551	0·13 (0·01–391)	48	0·33 (0·01–34)	1·35 (0·01–4·75)‡
Polonium	132	0·66 (0·01–42)	0	. .	. .
Fission products	2	0·17, 0·18§	0	. .	. .
Tritium	254	0·71 (0·11–127)	2	0·24, 0·76§	<0·01 (0·00–>1000)‡
Enriched uranium*	88	. .	1	. .	0·97 (0·05–4·45)
Natural uranium*	607	. .	4	. .	0·41 (0·13–0·98)
Ruthenium*	15	. .	0	. .	. .
Any internal dose*	5203	. .	76	. .	1·14 (0·80–1·63)

*Uptake only, odds ratios compared births to fathers monitored or not monitored for these radionuclides adjusted for year of birth, social class, birth order, and paternal age.
†Profile likelihood based CI. ‡Odds ratio in relation to dose (100 mSv) adjusted for year of birth, social class, birth order, and paternal age. §Actual values since only two births.

Table 4: **Total internal preconceptional gonadal doses of ionising radiation (radiation-worker cohort)**

Nested case-control study

A case-control study was done within the cohort of radiation workers based on film-badge doses. The cases were all stillbirths to radiation workers; controls were livebirths to radiation workers (up to four per case), matched on sex and date of birth. Cases and controls with zero FBtotal were excluded.

A conditional logistic-regression analysis was done to investigate whether the risk of stillbirth increased after paternal preconceptional irradiation, after adjustment for the variables found to be significant in the cohort study. Fractional polynomials[28] modelled the variation in risk of stillbirth with father's age, because this is known to be J-shaped with a higher risk for younger and older fathers.[23] 95% CI were based on a quadratic approximation of the log likelihood. The final model was checked as above.

Results

Non-Sellafield cohort

The distribution of births by decade, social class, and birth order is shown in table 1. Sex was not a significant risk factor for stillbirth. The best fit for the change in stillbirth rate by year of birth was a cubic model, adjusted for social class and birth order (Pearson χ^2_{1022}=1005, p=0·64). The model predicted 99·9 stillbirths (96 observed) among children conceived by fathers who were subsequently employed at Sellafield and 18·1 stillbirths (21 observed) in children of non-radiation workers (figure 1).

Sellafield cohort

The distribution of livebirths and stillbirths to Sellafield employees by decade, social class, birth order, and paternal age is shown in table 2. Although the stillbirth rate in the non-radiation-worker cohort was non-significantly higher than that in the radiation-worker cohort, the standardised stillbirth ratio was 1·14 (95% CI 0·82–1·88), reflecting the lower social-class distribution and the greater proportion of births in the earlier period in the former group. The distribution of external and internal paternal preconceptional irradiation is shown in tables 3 and 4, respectively.

Risk of stillbirth with exposure to ionising radiation

For external ionising radiation, there was a significant positive association between both ASDtotal and ASD90 and stillbirth risk, both in adjusted and unadjusted analyses (table 5). The adjusted odds ratio per 100 mSv for ASDtotal was 1·24 (1·04–1·45, p=0·009) giving, for example, for the median value of 30 mSv an odds ratio of 1·24 to the power of (30/100), ie $1{\cdot}24^{(30/100)}$=1·07 (1·01–1·12) and, for 350 mSv, the dose at the 99th centile, an odds ratio of $1{\cdot}24^{(350/100)}$=2·14 (1·14–3·69). Despite the small numbers of stillbirths (n=73) the adjusted odds ratio per 100 mSv was significantly raised for all stillbirths after 1961 for which cause of death was available. For stillbirths with congenital anomaly (15; nine neural-tube defects, three hydrocephalus, one Down's syndrome, one multiple anomaly, one trisomy not otherwise specified) and, within this category, for those with neural-tube defects (nine; eight anencephalic, one spina bifida), the odds ratio was significantly raised (table 5).

There was no significant increase in stillbirth risk with the total preconceptional dose of internal ionising radiation or exposure to any individual radionuclide (table 4). There was no association between stillbirth risk and the 90-day preconceptional internal doses (results not presented).

Checks of the model

Extensive checks of the model of stillbirth risk in relation to ASDtotal showed no evidence of unmeasured risk factors, variation between fathers in the effect of ASDtotal, or familial effects. Internal adjustment for covariates (in contrast with the use of offsets) made little difference (ASDtotal odds ratio per 100 mSv 1·27 [1·06–1·50]).

The linear-logistic model was an acceptable fit (deciles of risk test, p=0·46). Removal of the birth with the highest ASDtotal (911 mSv)—a stillbirth—reduced the adjusted odds ratio per 100 mSv to 1·17 (0·96–1·39, p=0·058). This stillborn baby did not have a congenital anomaly and so was not influential in the higher adjusted odds ratio found for stillbirths after 1961 with congenital anomalies (table 5). Exclusion of the livebirth with the highest ASDtotal increased for the odds ratio per 100 mSv to 1·25 (1·05–1·47, p=0·008). The doses for these births were checked and confirmed and no other births had undue influence. Exclusion of the stillbirths linked to a father by name made little difference (odds ratio per 100 mSv for ASDtotal 1·25 ([1·04–1·46], p=0·008).

	Odds ratio (95% CI)*	p†
1950–1989 ASDtotal (100 mSv)‡		
Unadjusted	1·30 (1·09–1·52)	0·003
Adjusted§	1·24 (1·04–1·45)	0·009
1950–1989 ASD90 (10 mSv)‡		
Unadjusted	2·50 (1·64–3·66)	<0·0001
Adjusted§	1·86 (1·21–2·76)	0·003
1961–1989 ASDtotal (100 mSv)§‖		
All stillbirths	1·26 (1·02–1·51)	0·018
Congenital anomaly	1·43 (0·93–1·94)	0·047
Neural-tube defects	1·69 (1·10–2·32)	0·011
Other specified cause	1·21 (0·94–1·49)	0·068

*Profile likelihood based CI. †Likelihood-ratio-test statistic.
‡9078 livebirths, 130 stillbirths. §Adjusted for year of birth, social class, and birth order by use of offsets from non-Sellafield cohort and for paternal age by use of national data.
‖7080 livebirths, 73 stillbirths.

Table 5: **Results of logistic-regression analysis of external preconceptional doses (radiation-worker cohort)**

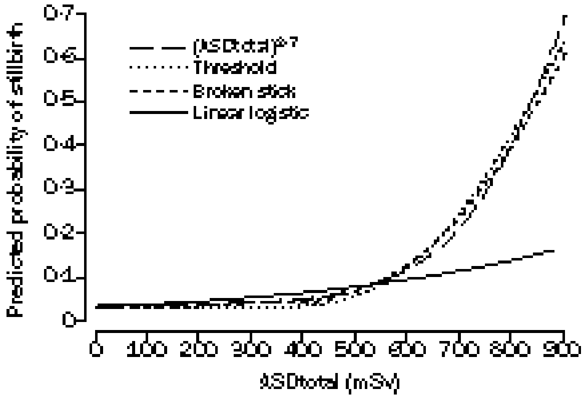


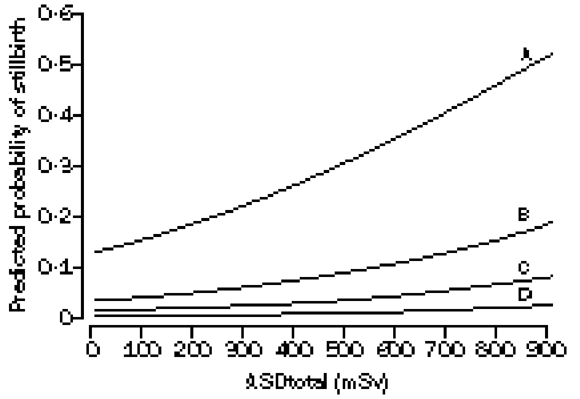
Figure 2: **Comparison of linear logistic, near quadratic, broken-stick, and threshold models for dose response**
For a first child, born in 1950, to a father aged 25 in social class III, manual.

Dose response

As a further part of the model-checking process the characteristics of the dose-response relation were explored. On the log scale the effect of dose was not significant and the model was a poorer fit than the other models (deviance=1314). The best fit (as indicated by the residual deviance) was with ASDtotal to the power of 2·7. However, there were so few fathers with high doses it would be unwise to prefer this model. The fits of the threshold and broken-stick models were not significantly better than that of the standard linear-logistic model (deviances of 1307, 1306, and 1309, respectively). For both these models, the break-point was estimated to be between 425 mSv and 450 mSv; above this dose the risk of stillbirth rose much more rapidly than in the standard model (figure 2). The linear-logistic model predicted that the risk of stillbirth increased with dose as shown in figure 3.

Attributable risk

Of the 130 stillbirths to radiation workers, the numbers attributable to paternal preconceptional irradiation for each model were: linear-logistic model, 17·5 stillbirths (3·1–31·9) ASDtotal$^{2·7}$ model, 4·5 stillbirths (0·7–8·3); threshold model, 2·3 stillbirths (0–4·8); broken-stick model, 9·8 stillbirths (0–26·5).



	Year of birth	Social class	Birth order	Paternal age (years)	Baseline probability (0 mSv)	Probability at 500 mSv	Odds ratio (95% CI)
A	1950	V	1	45	0·129	0·305	3·0 (1·2–6·5)
B	1989	V	1	45	0·030	0·085	3·0 (1·2–6·5)
C	1950	I	2	25	0·011	0·032	3·0 (1·2–6·5)
D	1989	I	2	25	0·002	0·007	3·0 (1·2–6·5)

Figure 3: **Predicted probability of stillbirth by total preconceptional external radiation dose (ASDtotal) in radiation worker cohort**

Nested case-control study

Within the nested case-control study the adjusted odds ratio for FBtotal was significant and similar to that for ASDtotal in the cohort analysis (odds ratio per 100 mSv=1·30 [1·03–1·66, p=0·014]). Exclusion of the highest dose stillbirth (936 mSv) gave odds ratio per 100 mSv of 1·23 (0·94–1·62, p=0·067).

The adjusted odds ratio for risk of stillbirth with FB90 was not significantly raised (odds ratio per 10 mSv=1·08 [0·68–1·74, p=0·370]). Although FB90 and ASD90 were highly correlated (r=0·84), linear regression showed a significant difference (p<0·001) between livebirths and stillbirths in the relation between FB90 and ASD90. FB90 were lower than ASD90 for stillbirths, but higher for livebirths. The significant difference was entirely due to the lower FB90 for the three stillbirths with the highest ASD90 and the higher FB90 for the three livebirths with the highest FB90. Exclusion of these six births (and in the case of the stillbirths, their controls), made little difference to the results for either FB90 (odds ratio per 10 mSv=1·16, 0·67–2·00, LRTS, p=0·301) or FBtotal (odds ratio per 100 mSv =1·29, 95% CI 1·01–1·63, LRTS, p=0·019). Scrutiny of the original dose records showed that the misclassification in ASD90 was a consequence of uneven dose accrual. As in the cohort study (table 4) there were no significant associations with either total internal dose or dose from any specific radionuclide.

Discussion

Stillbirth risk was significantly associated with total external paternal preconceptional irradiation in both the cohort and case-control studies. The risk was higher for stillborn babies with congenital anomalies, in particular those with neural-tube defects. In the cohort study there was also a significant association with ASD90, but no association was found with FB90 in the case-control study, suggesting that this may have been an artefact caused by the use of pro-rata 90-day dose estimates in the cohort study. There was no significant association with internal radiation exposure but the number of offspring to men with substantial internal exposures was small (table 4).

The study has some limitations. Livebirths and stillbirths to the workforce were linked by use of methods estimated as 98% accurate.[15] However, the linkage of stillbirths to the workforce was done twice and exclusion of the three cases with the weakest linkage information made no difference to the association with paternal preconceptional irradiation. Because cause of death has been recorded on stillbirth registration documents only since 1961, investigation of the risk of stillbirth by cause has been possible only since that date.

In regard to confounding of year of birth, paternal age, and paternal preconceptional irradiation, the stillbirth rate in Cumbria fell substantially during the period of the study, from 25 per 1000 births in 1950 to five per 1000 births in 1989. The effect of year was modelled by several different methods but none affected the significance of the association between paternal preconceptional irradiation and stillbirth risk. The final model of the year effect was a good predictor of the actual stillbirth rates. Since total external paternal preconceptional irradiation tended to be higher in the earlier decades of the study, there may have been some confounding by year of birth.[12] However, in the case-control analysis, where controls were matched on date of birth, the results were similar. Paternal age is a risk factor for stillbirth, with higher rates to younger and older fathers.[19] There was inevitably some confounding of age and total preconceptional radiation dose. However, analyses that excluded fathers over the age of 45 years produced almost unchanged odds ratios suggesting that most of the increased risk of stillbirth observed in older radiation workers (table 2) should be ascribed to paternal preconceptional irradiation rather than age.

The doses used in this study were collected prospectively as part of the routine monitoring of the workforce. Whereas they reflected best practice at the time and are thus the best available measurements of workforce exposure, film-badge dose estimates suffer from error of as much as 30%, though this has varied over time.[20]

The calculation of ASD90 pro rata from ASD assumes that radiation dose is accrued homogeneously over time, which is generally not so. With use of film-badge doses (case-control study) rather than ASD-based doses (cohort study), the association between 90-day preconceptional dose and stillbirth risk was lost. Total dose is a much more robust measure, and use of ASD or film-badge dose made little difference to the estimate of the association of ASDtotal with stillbirth risk.

The non-Sellafield model of stillbirth risk was an accurate predictor of the number of stillbirths in the two groups of children not included in the analyses. All the goodness-of-fit tests and other extensive model checks showed the final linear-logistic models of stillbirth risk to be a good fit to the observed data.

Statistical analysis showed no evidence of unmeasured factors influencing stillbirth risk and the models fitted the data well. However, we cannot completely exclude the possibility of confounding of paternal preconceptional irradiation with some other unmeasured risk factor for stillbirths.

This study is the largest and most comprehensive investigation of transgenerational effects in any workforce occupationally exposed to ionising radiation and is one of the few to use prospective dose measurements for each individual.[29] Only the study of the offspring of the atomic bomb survivors takes into account a more highly exposed group.[30] However, our study included comparatively few workers with high doses and the power to determine the form of dose-response was therefore limited.

In addition to the standard model, the relation between stillbirth risk and ASDtotal could have been modelled equally well by near-quadratic, threshold, or broken-stick models. However, because there were few births with high preconceptional doses, the study did not have sufficient power to discriminate between these various forms of dose-response.

One possible explanation of our findings is that irradiation caused genetic damage to the father's germ cells. Qualitatively consistent with this idea are observations of dose-response relations for death, congenital anomaly, and chromosomal damage in the offspring of preconceptionally irradiated male mammals, with outcome depending not just on total dose and dose fractionation but also on the interval between exposure and conception.[1–5,31,32]

Whereas the observed association of stillbirth risk and paternal preconceptional irradiation is qualitatively consistent with animal studies, the risk estimate is higher. Previous estimates of genetic risk in human beings, based on studies of irradiated rodents and their progeny, suggest that any heritable effect in the offspring of the Sellafield workforce would be small, with only one or two children affected in the first generation.[12] These estimates are based on the concept of genetic-doubling dose, for which several broad estimates are made, including that of the genetic and mutational component of the outcome in question, which for human disease is largely unknown.[32] However, current estimates of doubling doses are generally thought to be conservative.[32]

Stillbirths have a wide range of causes, including mechanical trauma during childbirth, but they may also result from overt congenital anomaly, the causes of which are known to include both environmental and genetic factors.[33] In our study, the increased risk was high for stillbirths with congenital anomalies and highest for those with neural-tube defects, eight out of nine of which were anencephaly. The causes of neural-tube defects are complex and include genetic, environmental, and dietary components.[33] The specific gene-environment interactions involved in anencephaly are distinct from those of other neural-tube defects.[33] Anencephaly has also been observed in the offspring of male irradiated mice[34] and has been reported in the offspring of men occupationally exposed to solvents,[35] suggesting that it may arise as a result of genetic damage in sperm. Men employed at Sellafield were exposed to a range of organic chemicals, though the extent to which these exposures are correlated with irradiation has not been reported.

The odds ratio for stillbirths in which congenital anomaly was not recorded was raised for the analysis after 1961, but, possibly because of the reduced power of this analysis, was of borderline significance (p=0·068). This category may include some stillbirths with congenital anomaly not recorded on the stillbirth registration document. It also includes stillbirths of unknown cause and others that resulted from premature labour or placental incompetence. Hence genetic or epigenetic factors may also have a role in some of these stillbirths.

The only study of heritable effects of irradiation in man of the scale of the present study is that of the offspring of the survivors of the atomic bombs in Hiroshima and Nagasaki. Between 1948 and 1954, the Atomic Bomb Casualty Commission collected information on 76 626 pregnancies longer than 20 weeks' duration to women in Hiroshima and Nagasaki.[30] This total included 4610 births to fathers with exposures greater than 10 mSv based on 1986 dose estimates, compared with 6809 in our study.[30] Despite the smaller size of the Japanese cohort, the total paternal collective preconceptional dose included in the study of untoward pregnancy outcomes of the atomic bomb survivors was greater (about 1835 person Sv) than that received by Sellafield fathers (about 529 person Sv).[30] The majority of analyses on those data, with either the original exposure groupings or the doses calculated in 1965 and again in 1986, showed a small non-significant trend to increasing untoward pregnancy outcome (non-malformed stillbirth, congenital anomaly, neonatal death) with increasing combined parental doses.[30] Analysis of the risk of adverse pregnancy outcome in the Japanese cohort has not been presented for paternal dose with just the 1986 dose estimates.

Unlike our study where exposures were measured prospectively, the doses to the bomb survivors were estimated retrospectively from a model based on location and shielding by buildings at the time of the blast and even the 1986 dose estimates suffer from random error of 40–50%, substantially reducing the statistical power of the analyses and hence leading to an underestimate of the magnitude and significance of the effect. However, in addition to the random error there were also systematic errors in the construction of the doses leading to consistent underestimates of dose and hence overestimates in dose effects.[36] The analyses were additionally restricted by the limited information on risk factors such as social class, known for only a subset of births. Direct comparison of the two studies is difficult because the bomb-survivor data were analysed by linear (additive) models whereas in our study logistic (multiplicative) models were used, which are considered to be more appropriate for the modelling of multifactorial processes.[37] However, the effect estimates reported by Otake and colleagues[30] for increased risk of stillbirth and congenital anomalies with combined parental radiation exposure in the offspring of men and women exposed to the atomic bombs in 1945, when applied to the Sellafield workforce, predict 0·9 (upper 95% CI 2·9) stillbirths (including those with congenital anomalies) attributable to parental irradiation. This compares with an attributable number in our study of between 0 and 31·9 stillbirths.

Sever and colleagues[29] did a case-control study of congenital anomalies in the vicinity of the Hanford nuclear reprocessing plant, USA. Individual dose data were used, although overall the doses were much lower than those in our study and only four fathers of case and control infants had doses higher than 150 mSv. Sever and colleagues found a near-significant association between paternal employment at Hanford before conception and congenital anomalies in offspring (one-tailed p between 0·05 and 0·10) and a significant association between paternal preconceptional exposure and neural-tube defects (n=11, p=0·02). They did not interpret the association as causal since, as in our study, the risk estimate observed was much higher than that expected from other studies, in particular those of the offspring of the bomb survivors. They were also concerned about an overall high rate of neural-tube defects around Hanford,[38] although they noted that rates of neural-tube defects were also reported to be high in Japan in the late 1940s and early 1950s. Investigation of stillbirth risk has not shown any overall excess in the immediate vicinity of Sellafield.[16,39] Scrutiny of the rates of stillbirth with neural-tube defects by postcode sector in Cumbria for 1961–89 showed no excess in sectors in which the affected children of radiation workers had been born.

There have been several other epidemiological studies investigating pregnancy outcome in the partners of irradiated men. Since the majority have involved small populations with low exposures, typically less than 200 mSv, it is perhaps not surprising that their findings have been inconsistent.

A comparable logistic-regression analysis of paternal exposure and pregnancy outcome in the Japanese data would allow more direct comparison and would allow, in addition, consideration to be made for the differences in the interval between exposure and conception in the two studies. A further study is planned that will involve ascertainment of deaths from congenital anomalies in liveborn children in Cumbria. In addition, the possibility of including children with non-lethal malformations and pregnancies terminated as a consequence of antenatal diagnosis is being explored.

Contributors

Louise Parker had the original idea for the study and together with Heather Dickinson, Mark Pearce, and Alan Craft was responsible for the study design and coding of stillbirth causes. Louise Parker and Heather Dickinson supervised the construction of the database. The analyses were done by Mark Pearce with involvement of Louise Parker and Heather Dickinson. Louise Parker, Heather Dickinson, and Mark Pearce wrote the paper after discussion with the other investigators. Murray Aitken reviewed the statistical analyses and supervised the model checking as well as commenting on the final drafts of the paper.

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Reference 2

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RESEARCH ARTICLE

The human sex odds at birth after the atmospheric atomic bomb tests, after Chernobyl, and in the vicinity of nuclear facilities

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Abstract
Background, aim, and scope Ever since the discovery of the mutagenic properties of ionizing radiation, the possibility of birth sex odds shifts in exposed human populations was considered in the scientific community. Positive evidence, however weak, was obtained after the atomic bombing of Japan. We previously investigated trends in the sex odds before and after the Chernobyl Nuclear Power Plant accident. In a pilot study, combined data from the Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Poland, and Sweden between 1982 and 1992 showed a downward trend in the sex odds and a significant jump in 1987, the year immediately after Chernobyl. Moreover, a significant positive association of the sex odds between 1986 and 1991 with Chernobyl fallout at the district level in Germany was observed. Both of these findings, temporality (effect after exposure) and dose response association, yield evidence of causality. The primary aim of this study was to investigate longer time periods (1950–2007) in all of Europe and in the USA with emphasis on the global atmospheric atomic bomb test fallout and on the Chernobyl accident. To obtain further evidence, we also analyze sex odds data near nuclear facilities in Germany and Switzerland.
Data and statistical methods National gender-specific annual live births data for 39 European countries from 1975 to 2007 were compiled using the pertinent internet data bases provided by the World Health Organization, United Nations, Council of Europe, and EUROSTAT. For a synoptic re-analysis of the period 1950 to 1990, published data from the USA and from a predominantly western and less Chernobyl-exposed part of Europe were studied additionally. To assess spatial, temporal, as well as spatial–temporal trends in the sex odds and to investigate possible changes in those trends after the atomic bomb tests, after Chernobyl, and in the vicinity of nuclear facilities, we applied ordinary linear logistic regression. Region-specific and eventually changing spatial–temporal trends were analyzed using dummy variables coding for continents, countries, districts, municipalities, time periods, and appropriate spatial–temporal interactions.
Results The predominantly western European sex odds trend together with the US sex odds trend (1950–1990 each) show a similar behavior. Both trends are consistent with a uniform reduction from 1950 to 1964, an increase from 1964 to 1975 that may be associated with delayed global atomic bomb test fallout released prior to the Partial Test Ban Treaty in 1963 and again a more or less constant decrease from 1975 to 1990. In practically all of Europe, including eastern European countries, from 1975 to 1986, and in the USA from 1975 to 2002, there were highly significant uniform downward trends in the sex odds with a reduction of 0.22% to 0.25% per 10 years. In contrast to the USA, in Europe there was a highly significant jump of the sex odds of 0.20% in the year 1987 following Chernobyl. From 1987 to 2000, the European sex odds trend reversed its sign and went upward, highly significantly so, with 0.42% per 10 years relative to the downward trend before Chernobyl. The global secular trend analyses are corroborated by the analysis of spatial–temporal sex odds trends near nuclear facilities (NF) in Germany and Switzerland. Within 35 km distance from those NF, the sex odds increase

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significantly in the range of 0.30% to 0.40% during NF operating time.

Conclusions The atmospheric atomic bomb test fallout affected the human sex odds at birth overall, and the Chernobyl fallout had a similar impact in Europe and parts of Asia. The birth sex odds near nuclear facilities are also distorted. The persistently disturbed secular human sex odds trends allow the estimation of the global deficit of births in the range of several millions.

Keywords Atomic bomb test · Chernobyl · Distance trend analysis · Ecological study · Environmental health · Environmetrics · Logistic regression · Low-level ionizing radiation · Male proportion · Nuclear facility · Radiation epidemiology · Radiation-induced genetic effect · Sex ratio · Spatial–temporal analysis

1 Introduction

1.1 Detrimental reproductive effects

In recent years, evidence and concern that exposure to the great diversity of chemical or physical occupational and environmental pollution has detrimental reproductive effects increased. Among those factors considered are endocrine disruptors, persistent chlorinated or brominated organic pollutants, and non-ionizing and ionizing radiation (James 1994). It has been demonstrated that prenatal exposure to some pesticides can adversely affect male reproductive health in animals. A possible association between maternal exposure to organochlorine compounds used as pesticides and cryptorchidism among male children has been investigated recently (Damgaard et al. 2006; Shen et al. 2008).

1.2 Sex odds as a reproductive health indicator

According to Neel and Schull (1991), the sex odds is unique among the genetic indicators. Its uniqueness arises from the fact that maternal exposure would be expected to produce an effect different from paternal exposure. For methodological reasons, we prefer “sex odds” over “sex ratio” (see Section 2.4). When investigating changes in the sex odds, a number of determinants of this trait have to be taken into account (Maconochie and Roman 1997; Jacobsen et al. 1999). However, when undisturbed, the birth sex odds is remarkably constant (Ein-Mor et al. 2010). According to James (1997), “ionizing radiation is the only reproductive hazard, which causes” (irradiated) “men to sire an excess of sons”. Conversely, irradiated mothers, so the theory goes (Schull and Neel 1958), would give birth to an increased proportion of girls. Therefore, one may anticipate eventual changes in the overall sex odds after local or global releases of genotoxic pollutants in case the presumed disturbances of the sex odds were not completely balanced between to the two genders of exposed parents.

1.3 Sex odds and chemical pollutants

Altered human sex odds at birth may be indicative of general health detriment or genetic damage under untoward environmental conditions for parents before conception, embryogenesis, pregnant women, or the fetus (Mocarelli et al. 2000; James 2006; Beratis et al. 2008; James 2008, 2010; Ruckstuhl et al. 2010). A distinct, however unexplained, seasonality of the monthly sex odds was reported by Lerchl (1998). Maternal exposure to polychlorinated biphenyls (PCBs) may be detrimental to the success of male sperm or to the survival of male embryos. Findings could be due to contaminants contained in industrial PCB products to metabolites of PCBs or to PCBs themselves (Hertz-Picciotto et al. 2008). Hence, more girls were born. In a commentary entitled “Where the boys aren’t: dioxin and the sex ratio”, Clapp and Ozonoff (2000) summarized the results of several studies where the exposure to dioxins entailed an alteration of the sex odds towards fewer boys. Hence, more girls were born. In a study performed in the state of Michigan in a well-defined period of PBB or PCB parental exposure, the odds of a male birth increased (Terrell et al. 2009). Hence, more boys were born.

1.4 Sex odds and statistical inference

While being easily accessible, the sex odds is often difficult to measure with sufficient precision for the scientific inquiry in mind. An important, however often neglected, aspect in the analysis of gender proportions is the number of cases considered and the resulting statistical power or precision. As a sobering rule, most publications on the human sex odds do not contain any information concerning the statistical power of the study. Consequently, positive results often fail to be replicated in subsequent investigations, resulting in irrelevant work due to low statistical power (Boklage 2005). On a population level, available datasets are large, with sizes in the range of hundreds of thousands or even millions. However, interesting differences in the sex odds may be small, in the range of a few tenth of a percent to a few percent. Even for 100,000 exposed and 100,000 non-exposed births, the power is only 54% to detect an increase from a normal sex odds of 1.06 to a disturbed sex odds of 1.08. Nevertheless, approximately 900 female concepti are affected detrimentally in the hypothetical situation of a disturbed sex odds of 1.08 in 100,000 exposed births under the conservative assumption that only the female gender was susceptible (Scherb and Voigt 2009).

1.5 Sex odds and other genetic traits and ionizing radiation

Following the explosions of the atomic bombs on Hiroshima and Nagasaki in 1945, an attempt had been made to organize an ongoing project on human genetics. Experiences after those bombings yielded some, but not entirely convincing, evidence of a certain shift in the human sex odds at birth (Schull and Neel 1958; Vogel and Motulsky 1986). The atmospheric atomic bomb tests, essentially terminated in 1963, injected huge amounts of radioactive materials into the biosphere. Radiation-induced genetic effects in rodents (fetal death in the offspring in utero) were observed by Luning et al. (1963), and radiation-induced genetic effects in humans (perinatal mortality and infant mortality) were reported by Sternglass (1971) and Whyte (1990). Based on these observations, a report of the European Committee on Radiation Risk (2003) drew further attention to the effects of the weapons fallout on infant mortality and concluded that there was a significant 2–3% increase per milliSievert of exposure over the 5-year period 1959–1963. This corresponds to a relative risk of 1.1 to 1.2/mSv per year. Consequently, these findings are in the same order of magnitude as the results reported by Scherb and Weigelt (2003). The ecological dose-specific relative risks for stillbirths and several distinct birth defects were in the range of 1.3 to 2.3/mSv per year.

The Chernobyl catastrophe has also created concern regarding the genetic effects of ionizing radiation resulting from fallout dispersed over large parts of Europe in Spring and Summer 1986 (Dubrova et al. 2002; Lazjuk et al. 2003). Although it has long been recognized by the scientific community that congenital malformation, stillbirth, neonatal death, and a disturbed human sex odds at birth are possible adverse genetic effects of ionizing radiation (Sperling et al. 1991; Neel et al. 1989; Dickinson et al. 1996; James 1997; Schull and Neel 1958; Padmanabhan et al. 2004; Muller 1927; Schull et al. 1966, 1981), there has been practically no national or international effort to thoroughly investigate genetic consequences after Chernobyl. The Chernobyl accident entailed radioactive exposure of large populations that varied substantially in time and in space as well, creating a new situation for epidemiology. We developed a spatial–temporal methodology for analytical ecological studies based on logistic regression to identify exposure response relations of untoward pregnancy outcomes in spatially stratified time series (Scherb and Voigt 2007, 2009; Scherb and Weigelt 2003). Particularly suited for epidemiological studies on radiation-induced genetic effects is the sex odds, i.e., the ratio of male to female human live births in a given region or time period.

Utilizing spatial–temporal approaches, long-term dose-dependent impacts of radioactive fallout after Chernobyl on stillbirths, birth defects, and the human sex odds at birth have been found. For example, nearly all published data concerning Down's syndrome show long-term increases after Chernobyl (Zatsepin et al. 2004; Sperling et al. 1994; Metneki and Czeizel 2005; Bound et al. 1995; Ramsay et al. 1991). Significant ecological relative risks for stillbirths and birth defects are in the range of 1.005 to 1.020/kBq m^{-2} ^{137}Cs. A relative risk coefficient of 1.010/kBq m^{-2} ^{137}Cs translates to a preliminary relative risk coefficient of 1.60/mSv per year (Scherb and Weigelt 2003). Furthermore, there are striking jumps or changes in slope (broken sticks) in the secular human birth sex odds trends in 1987 in practically all central and eastern European countries. No jumps or less pronounced jumps in the sex odds trends are visible in less exposed western European countries (e.g., France, Portugal, Spain) and in the USA. More specifically, superimposed on a downward trend in male proportions in the combined Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Poland, and Sweden between 1982 and 1992, there was a significant upward jump in the sex odds in 1987 of 0.47%. A positive association of the male proportion in Germany between 1986 and 1991 with radioactive exposure at the district level is reflected by an increase in the sex odds of 1.45%/mSv per year (Scherb and Voigt 2007). Consequently, a long-term chronic impact of radioactive fallout on the secondary sex odds has been found.

1.6 Aim and scope

In our paper, we will analyze sex odds data with respect to global atmospheric atomic bomb test fallout, with respect to fallout due to nuclear accidents and with respect to radioactive releases of nuclear facilities (NF) under normal operating conditions. We synoptically study sex odds time trends in the USA and in a predominantly western European data set from 1950 to 1990 considering the possibility that those trends could have been disturbed by the delayed atmospheric atomic bomb test fallout globally released prior to the atmospheric atomic bomb test ban in 1963 (Partial Test Ban Treaty—PTBT). Then, we analyze essentially complete European sex odds trends from 1975 to 2007 with emphasis on the Chernobyl accident. Moreover, we will extend and re-analyze recently published data on spatial trends of the sex odds in the vicinity of nuclear facilities (including nuclear power plants) in Germany and Switzerland (Kusmierz et al. 2010).

2 Data and statistical methods

2.1 Europe and USA 1950 to 1990

For the synoptic re-analysis of the USA data and the western European data, we used figures published by Martuzzi et al. (2001) and Mathews and Hamilton (2005). A disadvantage of the European data published by Martuzzi et al. with respect to the Chernobyl issue is the restriction to only 23 European countries with predominantly western and less eastern European coverage (in Martuzzi et al., Czechoslovakia counts one country and Germany counts two countries: FRG and GDR; in our data, it is the other way around). The complement of our essentially complete "Europe" (39 countries; see Section 2.2) and the one by Martuzzi et al. consists of Albania, Belarus, Estonia, Latvia, Lithuania, Luxembourg, Malta, San Marino, The Russian Federation, Ukraine, and Yugoslavia. However, for a secular global synoptic analysis of the European and USA sex odds trends, 1950 to 1990, the Martuzzi et al. data are informative and sufficient.

2.2 Europe 1975 to 2007 and USA 1975 to 2002

This portion of our study is based on official, national, and gender-specific annual live births statistics compiled and provided by the WHO, United Nations, Council of Europe, and EUROSTAT, e.g., the data base http://data.euro.who.int/hfadb managed within the WHO framework 'health for all data base (hfadb)' turned out to be especially useful, complete, and user-friendly. In Table 1, we list 39 European countries with complete data from 1975 to 2007. Note that the former Czechoslovakia now comprises two and the former Yugoslavia six countries. For some republics of the former Soviet Union, no gender-specific birth data were available prior to 1980. As there are two such republics with territory in Europe, Kazakhstan and Moldova, those republics had to be excluded from the overall European trend analysis from 1975 to 2007. Also, no data or essentially incomplete data were available for Andorra, Liechtenstein, Monaco, Turkey, and Vatican. In case of incomplete, inconsistent, or doubtful data, the corresponding national statistical offices were successfully asked for help in several instances. Note that most data in Table 1 originate from the "hfadb" Internet data base by the WHO. The US data from 1975 to 2002 were again obtained from Mathews and Hamilton (2005).

2.3 German and Swiss municipalities 1969 to 2009

Kusmierz et al. (2010) compiled official gender-specific annual live births statistics for all municipalities in Switzerland and for all municipalities in the following states of Germany: Baden-Württemberg, Bavaria, Lower Saxony, North Rhine-Westphalia. For Rhineland-Palatinate, provisional data at the level of 36 districts only were available at that time. As we are now able to extend the data set utilizing 2,312 municipalities of Rhineland-Palatinate instead of the corresponding 36 districts (Table 2), a more powerful analysis can be carried out. To calculate the distances of the municipalities from nuclear facilities, we determined uniform coordinates for the geographic positions of those municipalities including the geographic positions of 28 pertinent nuclear facilities including all nuclear power plants in Germany and Switzerland (Kusmierz et al. 2010). All in all, our extended data set comprises 9,596 municipalities, 361,056 municipality-years, and 20.4 million live births with a total sex odds of 1.0552 (Table 2).

2.4 Statistical methods

To assess time trends in the occurrence of boys among all live births and to investigate whether there have been significant changes in the trend functions in 1987 or later, we applied ordinary linear logistic regression. This involves considering the male proportion among all male (m) and female (f) births: $p_m = m/(m + f)$. The important and useful parameters in this context are the sex odds: SO = $p_m/(1-p_m) = m/f$, and the sex odds ratio (SOR), which is the ratio of two interesting sex odds if those two sex odds have to be compared, e.g., in exposed versus non-exposed populations. We used dummy coding for single points in time and for time periods as well. For example, the dummy variable for the time window from 1987 on is defined as $d_{87}(t)=0$ for $t<1987$ and $d_{87}(t)=1$ for $t \geq 1987$. The simple and parsimonious logistic model for a trend and a jump in 1987 has the following form (LB = live births):

$$\text{Boys}_t \sim \text{Binomial}(\text{LB}_t,\ \pi_t)$$
$$\log \text{odds}(\pi_t) = \text{intercept} + \alpha * t + \beta * d_{87}(t)$$

To allow for changing sex odds trend slopes (broken sticks) after Chernobyl, we used dummy coding of time windows and interactions of those time windows with time. The data in this study were processed with Microsoft Excel 2003. For statistical analyses, we used R 2.11.1, MATHEMATICA 5.0 and mostly SAS 9.1 (SAS Institute Inc.).

3 Results

3.1 Analysis of European and US data 1950 to 1990

The Chernobyl accident and its possible consequences have sometimes been discussed in perspective of the experiences

Table 1 European gender-specific live births from countries with complete data from 1975 to 2007; USA from 1975 to 2002 (Mathews and Hamilton 2005)

Country	Births 1975–2007			
	Country number	Male	Female	SO
Albania	1	1,130,199	1,040,746	1.0860
Austria	2	1,458,550	1,386,074	1.0523
Belarus	3	2,170,667	2,050,534	1.0586
Belgium	4	2,060,708	1,955,233	1.0539
Bulgaria	5	1,686,699	1,595,331	1.0573
Czechoslovakia (f.)	6–7	3,396,664	3,222,748	1.0540
Denmark	8	1,057,854	1,003,118	1.0546
Estonia	9	314,547	297,105	1.0587
Finland	10	1,045,181	998,718	1.0465
France	11	12,840,000	12,210,308	1.0516
Germany	12	13,488,891	12,774,421	1.0559
Greece	13	1,977,369	1,850,287	1.0687
Hungary	14	2,099,904	1,988,257	1.0562
Iceland	15	72,914	69,321	1.0518
Ireland	16	1,024,334	966,373	1.0600
Italy	17	10,120,009	9,542,422	1.0605
Latvia	18	507,329	481,021	1.0547
Lithuania	19	779,998	740,959	1.0527
Luxembourg	20	82,544	77,845	1.0604
Malta	21	85,225	79,638	1.0702
Netherlands	22	3,174,069	3,023,245	1.0499
Norway	23	950,341	900,220	1.0557
Poland	24	9,007,557	8,496,847	1.0601
Portugal	25	2,201,456	2,061,412	1.0679
Romania	26	5,148,669	4,876,409	1.0558
Russian Federation	27	30,980,409	29,371,349	1.0548
SanMarino	28	2,988	2,757	1.0838
Spain	29	7,938,940	7,425,565	1.0691
Sweden	30	1,721,411	1,627,973	1.0574
Switzerland	31	1,305,459	1,238,886	1.0537
Ukraine	32	10,118,805	9,572,157	1.0571
United Kindom	33	12,371,861	11,741,276	1.0537
Yugoslavia (f.)	34–39	5,170,407	4,832,146	1.0700
All European		147,491,958	139,500,701	1.0573
USA (1975 to 2002)		54,256,593	51,683,339	1.0498

f. former

after the atomic bombings of Japan in World War II and the above-ground atomic bomb tests from 1945 to 1963, the year of the PTBT. Therefore, an analysis of the human birth sex odds before and after the atmospheric atomic bomb tests is also self-evident. Figure 1 displays the trends of the live births sex odds in Europe and in the USA published by Martuzzi et al. (2001) and by Mathews and Hamilton (2005), respectively. The synoptic analysis behind Fig. 1 is based on 420 million births and covers the period from 1950 to 1990. Both trends are similar in that they are consistent with a uniform reduction from 1950 to 1964, an increase from 1964 to 1975, and again a more or less constant decrease from 1975 to 1990. We conjecture that the increases in Europe and USA are a consequence of the globally emitted and dispersed atmospheric atomic bomb test fallout prior to the test ban in 1963 that affected large human populations overall after a certain delay. The synoptic trend components are highly significant ($p<0.0001$) due to the large number of births involved.

3.2 Analysis of European data 1975 to 2007 and US data 1975 to 2002

Figure 2 presents the sex odds trends of the USA from 1975 to 2002 and the corresponding European trend from 1975

Table 2 Gender-specific live births that are available from Germany and Switzerland at the municipality level

Region	Municipality	Available	Municipality-years	Births	Male	SO
Baden-Württemberg	1,102	1975–2008	37,468	3,498,211	1,795,839	1.0549
Bavaria	2,056	1972–2008	76,072	4,366,993	2,241,831	1.0549
Lower Saxonia	1,024	1971–2009	39,936	2,927,455	1,503,478	1.0558
North Rhine-Westphalia	396	1980–2008	11,484	5,033,665	2,584,664	1.0554
Rhineland-Palatinate	2,312	1972–2009	87,856	1,404,742	721,059	1.0547
Switzerland	2,706	1969–2008	108,240	3,182,400	1,633,929	1.0552
Combined	9,596		361,056	20,413,466	10,480,800	1.0552

to 2007. The synoptic analysis behind Fig. 2 is based on 393 million births. In the USA, we can see a rather smooth, uniform, and undisturbed downward trend during the whole time span of 28 years. The trend is a highly significant reduction of the sex odds of 0.22% per 10 years, 95% CI (0.17, 0.27), $p<0.0001$. In Europe, from 1975 to 1986, compared to the USA, we can see a similar downward trend with a sex odds reduction of 0.25% per 10 years (0.14, 0.35), $p<0.0001$. In contrast to the USA, in Europe in the year 1987 following Chernobyl, there was a highly significant jump of the sex odds of 0.20% (0.10, 0.30), $p=0.0001$. From 1987 to 2000, the European sex odds trend changed its sign and went upward relative to the downward trend before Chernobyl with 0.42% per 10 years (0.34, 0.51), $p<0.0001$. From 2000 onward, the European trend changed its sign again then decreased with 0.48% per 10 years (0.24, 0.71), $p<0.0001$. This means that we detected a significant gender gap in Europe after Chernobyl whereas no such similar effect is seen in the USA less exposed by Chernobyl fallout.

The question immediately arises whether the jump and the trend reversal in the European sex odds after Chernobyl (1986) are caused by the ionizing radiation released. Evidence of causality is strengthened if the disturbance of the sex odds trends were stronger or weaker in countries with more or less Chernobyl fallout, respectively. This can easily be checked by considering medium-sized or large countries with sufficient statistical power at lower or greater distances from Chernobyl, e.g., France, Germany, and the Russian Federation. Figure 3 shows these data, including appropriate parsimonious jump models. Whereas there is practically no jump in 1987 in France (sex odds ratio of jump (SOR)=1.0003; $p=0.8489$), there is after all a noticeable, however insignificant, jump in Germany (SOR=1.0019; $p=0.2133$) and an extremely significant jump in the Russian Federation (SOR=1.0088; $p<1.0\text{E}{-25}$). Because France was less exposed than Germany and Germany was less exposed than the Russian Federation (Drozdovitch et al. 2007), we observe a qualitative dose–response association between the fallout levels and the sex odds jump heights from 1987 onward. Together with the fact that the jumps in the sex odds trends follow the exposure in time, strong evidence of causality is obtained. A formal and quantitative dose–response analysis at the district level in Germany yielding a preliminary ecological SOR/mSv per year of 1.0145 has previously been published (Scherb and Voigt 2009, 2007).

3.3 Further evidence: increased sex odds near nuclear facilities

A significantly elevated human sex odds at birth has been found in the vicinity (< 35 km) of nuclear facilities in Germany and Switzerland (Kusmierz et al. 2010). In this

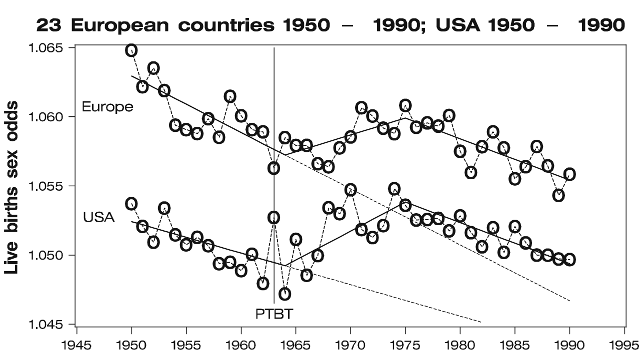

Fig. 1 Trends of the live births sex odds (male/female) in Europe and in the USA, 1950 to 1990 (Martuzzi et al. 2001; Mathews and Hamilton 2005)

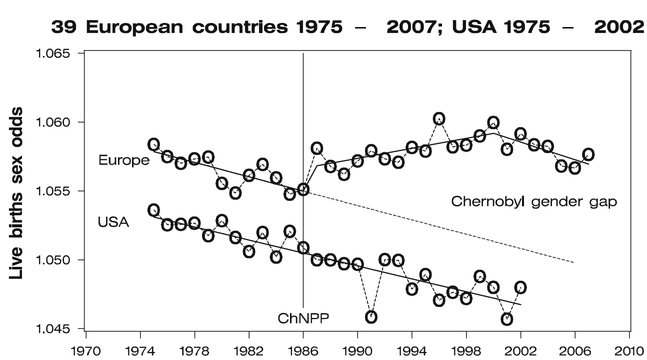

Fig. 2 Trends of the live births sex odds (male/female) in the USA, 1975 to 2002, and in 39 European countries; see Table 1 and Mathews and Hamilton (2005)

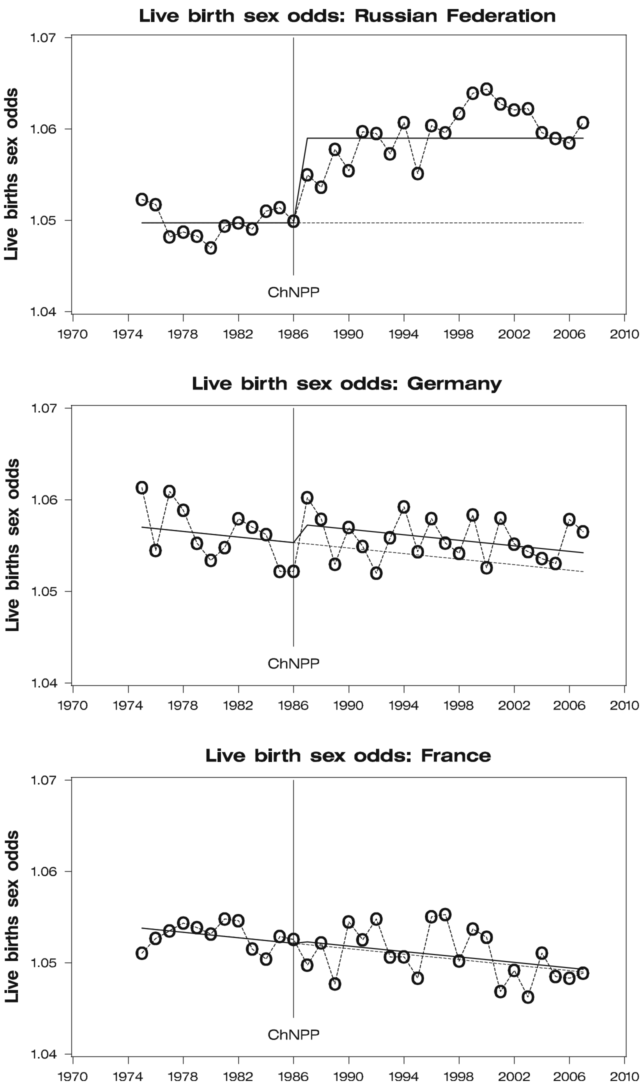

Fig. 3 Trends of the live births sex odds (male/female) in France, Germany, and the Russian Federation

paper, we improved the data base (see Section 2.3), resulting in a somewhat more powerful analysis displayed in Fig. 4. The simple jump model for distances below 35 km yields a sex odds base-line level of 1.0543, 95% CI (1.0532, 1.0553) and a sex odds ratio for the jump at 35-km distance of 1.0036, 95% CI (1.0015, 1.0056), p=0.0003. Using a more impartial Rayleigh function (p=0.0014), the estimated sex odds peaks at 14.3 km, 95% CI (9.1, 19.5) with a SOR peak=1.0052, 95% CI (1.0022, 1.0082). This finding qualitatively supports the recently reported increased childhood cancer and childhood leukemia incidences near nuclear power plants in Germany (Spix et al. 2008; Nussbaum 2009). A sensitivity analysis displacing all nuclear facilities' original geographic positions 50 km to the west or 50 km to the east yields insignificant (p>0.5) Rayleigh functions (Fig. 5). One may expect such a behavior in case a real causation by NF was indeed behind the observed significant effects in Fig. 4, and no corresponding causative agent is present at arbitrary dummy locations without nuclear facility installations.

3.4 More or less boys or girls?

In this section, we address the question on whether there is empirical evidence that the increased male birth proportions after the atomic bomb tests, after Chernobyl, and in the vicinity of nuclear facilities are in fact due to a reduced frequency of female births and not due to an increased number of male births. In principle, it seems reasonable to assume that, if radioactive fallout has any influence on human reproductive health at all, it would not increase the number of live births relative to a prevailing (positive or negative) live births trend in a given region or time period. Indirect evidence of somewhat decreased live births results from increased spontaneous abortions observed in Finland (Auvinen et al. 2001) and from increased stillbirth proportions in several parts of Europe after Chernobyl (Scherb et al. 1999). An obvious approach is the inspection of trends of absolute numbers of gender-specific births. An interesting example is Denmark. Figure 6 shows the gender-specific live births trends in Denmark from 1984 to 1990. In this period of monotonically increasing births, we notice certain impressions of the male and female trend functions, especially in 1987 and 1988. Compared to the hypothetically undisturbed straight and parallel trend lines, there were deficits of approximately 500 male and approximately 1,800 female births from 1986 onward. This yields a raw and very preliminary estimate of the sex odds in the hypothetical deficit of births in Denmark of 3/10. Admittedly, this is a crude approach, but it may nevertheless be a valid consideration. However, it is also possible that fear to conceive after Chernobyl led to this apparent deficit of births in Denmark, and if the decision not to conceive was associated with several sex-determining factors in the population (age, social class, etc.), the difference between the male and female birth trends could be independent of ionizing radiation. Therefore, this observation has to be interpreted with care and further independent information concerning this issue should be sought. As yet, we have not found other countries with such a seemingly clear behavior. In most cases, the trends of absolute numbers of births are more irregular and less smooth compared to those Danish trends in Fig. 6.

With the assumption of a sex odds in the birth deficit of 3/10, all unknown parameters are determined and it is possible to estimate the apparent gender gaps in Figs. 1 and 2 by straightforward arithmetic. The combined European and USA gender gaps after the PTBT (1963) to 1990 in

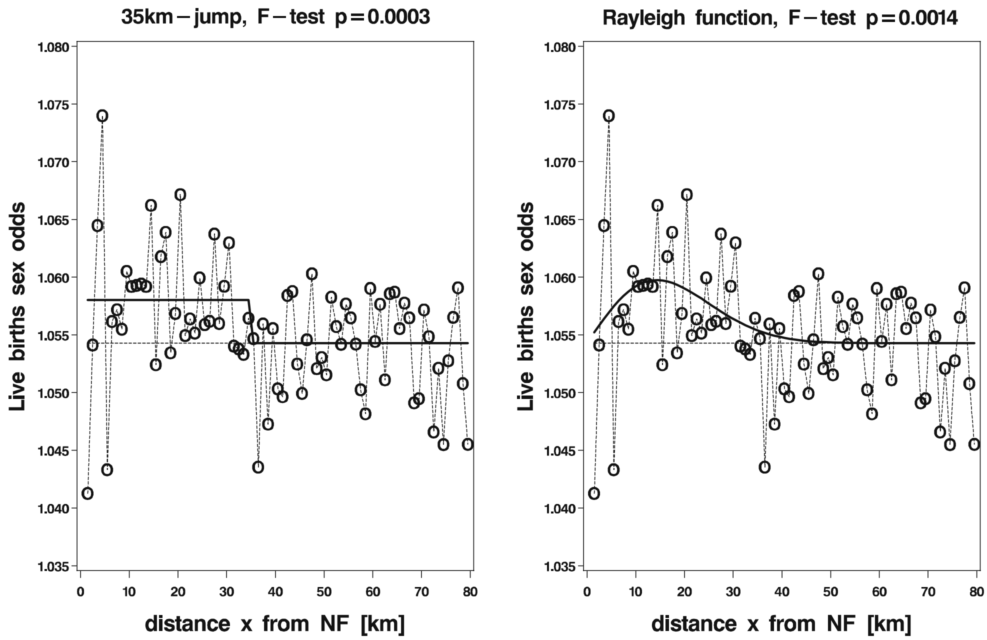

Fig. 4 Improved 35-km jump function and Rayleigh function models for the live births sex odds (male/female) depending on distance from nuclear facilities (NF) in Germany and Switzerland (Kusmierz et al. 2010)

Fig. 1 theoretically represent approximately 1.2 million children. Analogously, the European gender gap from 1987 onward to 2007 in Fig. 2 theoretically amounts to approximately 800,000 children.

Based on our previous analysis of birth defects and stillbirth after Chernobyl, i.e., assuming an approximate dose-specific relative risk of 1.5/mSv per year, it is possible to conjecture that the number of impaired children is in the same order of magnitude as the deficit of births after Chernobyl (Scherb and Weigelt 2003). Therefore, assuming that our approach is valid and realistic, it becomes clear that the deficit of births and the number of stillborn or impaired children after the global releases of ionizing radiation taken together may be in the range of several millions.

Note that our data yield only an incomplete account of contaminated regions and contaminated time periods on the globe. Given that the European and USA trends in Fig. 2 are both representative of the past as well as of the future, it seems possible that the deficit of births and the cumulative number of impaired children will still be increasing in many years to come because a complete recovery of the disturbed human sex odds is presently not foreseeable. However, a partial recovery is already visible by the significant downward trend in Europe from 2000 onward (Fig. 2).

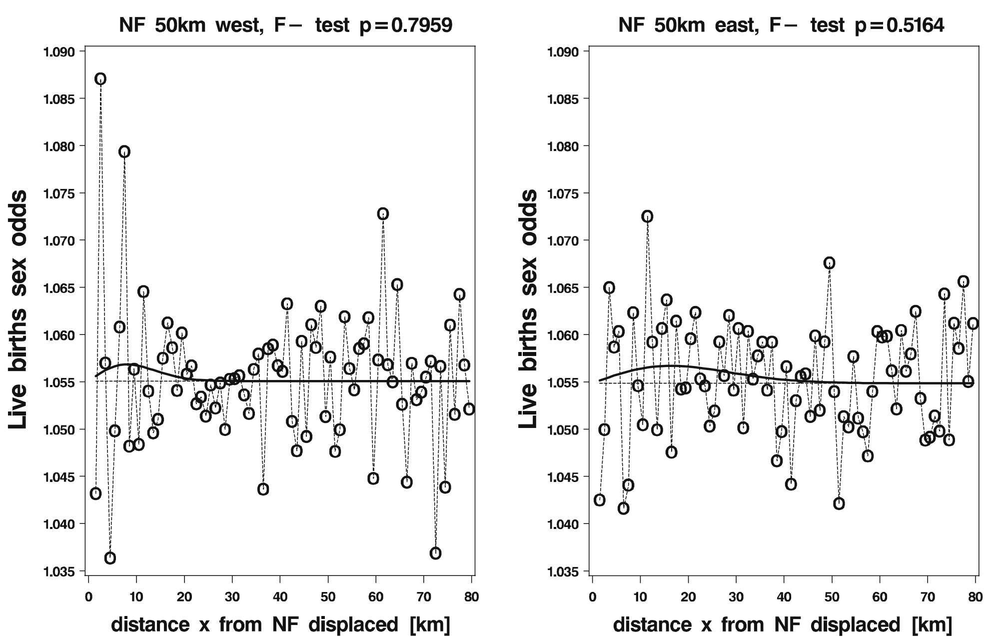

Fig. 5 Insignificant distance trends (Rayleigh functions) near fictitious positions of nuclear facilities NF obtained by dis placing all original positions of German and Swiss NF 50 km to the west (*left*) or 50 km to the east (*right*)

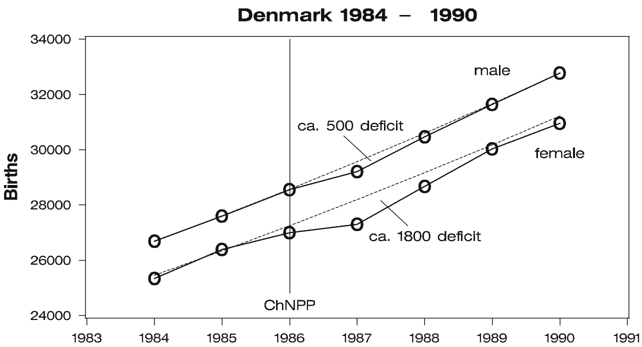

Fig. 6 Trends of gender-specific births in Denmark and preliminary estimation of the sex odds in the deficit of births: 500/1,800 ≈3/10

4 Summary and discussion

In this paper, we analyzed large data sets with respect to possible alterations of the human birth sex odds after local or global releases of ionizing radiation. The sex odds increase under elevated exposure to ionizing radiation. Straightforward time trend analyses of official and essentially complete USA and European gender-specific birth statistics reveal certain disturbances of the sex odds after the atmospheric atomic bomb testing on the whole globe, after the Chernobyl accident in Europe, and in the vicinity of nuclear facilities during their operating periods in Germany and Switzerland. It is unlikely that, among the many determinants of the sex odds discussed in the literature, any one single factor or several factors in common acted synchronously with the Chernobyl event from 1986 onward. Even if there were secular coincidences of other sex-determining factors with the aftermath of Chernobyl, it is unlikely that those factors occurred or changed in a parallel abrupt manner in 1987, the year immediately after this nuclear catastrophe in Europe. Therefore, because of its well-known mutagenic properties, ionizing radiation released by the atomic bomb tests, by the Chernobyl accident and by operating nuclear facilities, is the most parsimonious explanation for the disturbed birth sex odds trends observed.

Following the explosions of the atomic bombs on Hiroshima and Nagasaki, an attempt had been made to organize an ongoing project on human genetics (Vogel and Motulsky 1986). Experiences after the bombings yielded some, but not entirely convincing, evidence of a certain shift in the human sex odds at birth. For all categories, the sex odds showed changes in the expected direction: Under the assumption that only one parent was affected, irradiation of mothers would result in less male and irradiation of fathers would ensue less female offspring. However, based on the Hiroshima and Nagasaki data, it does not seem possible to predict the direction of an effect in case both parents or the conceptus had been exposed more or less uniformly. Vogel and Motulsky (1986) state: “When both parents were exposed, the maternal appeared to exceed the paternal effect.” However, with only approximately 12,000 exposed parents, this could as well have been a chance result because of insufficient statistical power (see “Section 1.4”). Our results concerning uniform exposures of very large populations consistently show increased sex odds. Moreover, this increase of the male proportion turned out to be dose dependent at the ecological level (Scherb and Voigt 2007). Dubrova et al. (2002) reported that the paternal mutation rate at eight minisatellite loci in exposed families from Ukraine is elevated, and they found no evidence of elevated mutation rates in the germline of exposed mothers: “A statistically significant 1.6-fold increase in the paternal mutation rate was found in the exposed families from Ukraine, whereas maternal mutation rate in this cohort was not elevated.” If one may speculate that the genetic information in fathers is more susceptible to damage by ionizing radiation compared to mothers, then one could perhaps explain why in uniformly irradiated populations the paternal effect exceeds the maternal effect with the consequence of more female than male lost concepti or children and, thus, increased sex odds.

5 Conclusions and outlook

Our observations add evidence to findings in the field of radiation epidemiology indicating considerably underestimated health risks of the so-called low-level (< 100 mSv) ionizing radiation (Bandazhevski et al. 2009; Ericson and Kallen 1994; Huether et al. 1996; Lazjuk et al. 2003; Muerbeth et al. 2004; Ramsay et al. 1991; Zatsepin et al. 2007; Auvinen et al. 2001; Wertelecki 2010). The International Commission on Radiological Protection (ICRP) has assessed the risk of severe hereditary diseases (e.g., hemophilia, Down’s syndrome) in a general population exposed to low doses and low dose rates. ICRP estimated a risk factor of 1 in 100 per Sievert for severe hereditary diseases appearing at any time in all future generations (i.e., relative risk per Sievert (Sv)=1.01). A more specific risk estimate, in the same order of magnitude however, has been propagated by the United Nations Scientific Committee on the Effects of Atomic Radiation (2001): “The estimate of risk” (at 1 Gy) “for congenital abnormalities is about 2,000 cases per million live births (compared to 60,000 cases per million live births).” Note that 1 Gy is equivalent to 1 Sv (Sievert) for gamma radiation. The UNSCEAR 2001 risk translates to a relative risk per Sievert of 1.03 (= 62,000/60,000). In sharp contrast to that, our estimated effects are in the order of magnitude of 1.50/mSv per year for birth defects and stillbirths and 1.02/mSv per year for the sex odds (Scherb and Voigt 2007; Scherb and Weigelt 2003).

This means that the internationally established radiation risk concept based on average absorbed dose is in error at three to four orders of magnitude or, more likely, it is conceptually wrong.

Our results suggest that the global deficit of births and the increased number of stillborn or impaired children due to the atmospheric atomic bomb tests and due to the Chernobyl catastrophe may be in the range of several millions. This is a large absolute number although it is a small relative number with respect to all births in the range of several hundreds of millions considered here, as well as with respect to risks like accidents, diseases, or naturally occurring unfavorable pregnancy outcomes, etc. However, the detected adverse genetic effects point to an enhanced impairment of humankind's genetic pool by artificial ionizing radiation. Moreover, our results contribute to disproving the established and prevailing belief (UNSCEAR 2000) that radiation-induced hereditary effects have yet to be detected in human populations.

We will focus our future research efforts on underestimated reproductive health effects associated with low-dose ionizing radiation by extending and specifying our spatial–temporal methodology. Further data sources will be explored with the aim of complementing our findings. Important data on neglected environmental and health topics are partly available. However, often there is no (optimum) utilization of the existing data bases. Thus, greater input from mathematicians and statisticians is urgently needed to scrutinize those data. To achieve this goal, the full spectrum of different data analysis approaches should be considered and applied appropriately. Improved interdisciplinary skills are needed at all stages of environmental health research. More research should be initiated to strengthen the evidence achieved and, importantly, to open minds to the danger of ionizing radiation.

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ABSTRACT

Intervention levels for emergency response are for national authorities to decide, but the latest information suggests that stable iodine prophylaxis for children up to the age of 18 years be considered at 10 mGy, that is 1/10th of the generic intervention level expressed in the *International basic safety standards for protection against ionizing radiation and for the safety of radiation sources*.

For adults over 40, the scientific evidence suggests that stable iodine prophylaxis not be recommended unless doses to the thyroid from inhalation are expected to exceed levels that would threaten thyroid function. This is because the risk of radiation induced thyroid carcinoma in this group is very low while, on the other hand, the risk of side effects increases with age.

The latest information on the balance of risks and benefits will also need to be properly considered in the plans for any distribution and storage of stable iodine. It suggests that stockpiling is warranted, when feasible, over much wider areas than normally encompassed by emergency planning zones, and that the opportunity for voluntary purchase be part of national plans.

Keywords

IODINE – therapeutic use
RADIATION INJURIES – prevention and control
DISASTER PLANNING
THYROID GLAND – physiology
GUIDELINES

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Preface

In 1989, the WHO Regional Office for Europe published *Guidelines for iodine prophylaxis following nuclear accidents*, primarily stimulated by the Chernobyl accident. This was, however, prior to the significant increase in cases of childhood thyroid cancer, first reported in Belarus in 1991 and verified by a mission from the Regional Office in 1992.

The geographical extent of ground contamination by ^{131}I following the Chernobyl accident had not been anticipated and, due to its relatively short half-life, was not fully realized even in 1989. Now it is clear that a population of roughly 2.3 million children living in southern Belarus, northern Ukraine and the most easterly regions of the Russian Federation was exposed to significant amounts of radioactive iodine. The result, less than fifteen years after the accident, is more than 1000 cases of thyroid cancer, most probably solely attributable to this single release of radioactivity to the environment.

The decision to recommend the wide administration of stable iodine has to be taken only when there is certainty that more good will be achieved than harm. In this respect the experience of Poland, in employing stable iodine prophylaxis on a large scale (17 million doses distributed, 10 million to children) and evaluating the side effects, has been crucial in the decision to issue these Guidelines.

These Guidelines are based on a consultation with a wide range of experts in the relevant disciplines and are endorsed by three out of the four regional thyroid associations.

The sensitivity of the child's thyroid to the carcinogenic effects of radiation represents a significant public health risk in the event of exposure to radioactive iodine. With effective planning and the use of stable iodine prophylaxis, in association with other preventive measures, this risk is to a large degree avoidable.

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Foreword

In 1989, the WHO Regional Office for Europe issued *Guidelines for iodine prophylaxis following nuclear accidents* at the instigation of two Member States, Switzerland and the United Kingdom. These Guidelines were based on a Workshop discussion and comments by specialized reviewers and provided authoritative and practical guidance on all aspects of iodine prophylaxis as it applies to nuclear emergencies.

In 1991, the first indications of a marked increase in childhood thyroid cancer became apparent in Belarus and then in the Russian Federation and Ukraine. These countries were closest to the Chernobyl accident. When the seriousness of this increase became clear beyond doubt, and the results of the administration of stable iodine to the child population of Poland immediately after the accident, were available, WHO convened a small expert group *(1)* to advise on the need to revise the Guidelines. As a result, two consultants (Dr Wendla Paile and Mr Leif Blomqvist) were asked to prepare a revised document based on the views expressed at that expert group meeting. Following consultation with WHO headquarters in Geneva and the International Atomic Energy Agency (IAEA) in Vienna, several expert reviewers were consulted *(2)*. The comments were reviewed by the consultants and the WHO and IAEA secretariats and the document accordingly amended. A final formal review of the document took place in association with the annual American Thyroid Association meeting in Portland, Oregon, USA in September 1998 *(3)*. Each of the four regional thyroid associations were invited to nominate two experts and the IAEA nominated two additional participants. Following the Oregon meeting, the regional thyroid associations were invited to endorse the document and three – the ETA, the OATA and the LATS – agreed to do so.

Stimulated by the reports of increased thyroid cancer the research community has made much progress in understanding the nature of radiation-induced thyroid cancer and its dependence on age at exposure. It became clear that in order to protect public health it would be necessary to intervene at lower doses for children and young people aged up to and including 18 years at exposure than for young adults. In contrast, older adults would have little benefit from iodine prophylaxis to avert comparatively low doses, while being subject to higher risks of side effects. The revised document, therefore, departs from its predecessor in giving advice on how to obtain optimal protection of public health in the application of the presently recommended generic intervention level of 100 mGy, applied independently of age, to the practical circumstances where young and older adults are potentially exposed to radioactive iodine.

The present document, therefore, provides an authoritative update to the advice issued by the WHO Regional Office for Europe in 1989.

The aims and objectives of the document are:

- from the public health perspective:
  - to summarize the current assessment of the benefits and risks of stable iodine prophylaxis to block the uptake by the thyroid gland of radioactive iodine released to the environment in accidents and emergencies;
  - to provide information on appropriate dosage and contraindications for the administration, as a public health measure, of stable iodine to various population groups;
- from the emergency preparedness perspective:
  - to aid the planning for such an administration in an emergency; and
  - to give guidance on the practical aspects of the storage and distribution of stable iodine.

The potential readership of the document includes:

- public health authorities and physicians at national and local levels
- nuclear emergency planners, emergency management personnel
- emergency aid administrators
- civil defence personnel.

The purpose of this document is to make available the latest information on the use of stable iodine prophylaxis in the context of radiation protection of the thyroid, and in particular as part of the emergency response preparedness for nuclear accidents. It should be stressed that it has no implications for the routine medical use of radioiodine in diagnosis and treatment of thyroid disorders.

In issuing this document, the World Health Organization welcomes comments from experts and institutions for further advice for future updating of the document.

1. Introduction

Despite rigorous safety systems, there remains a finite probability that an accident can occur in a nuclear reactor that can lead to the fuel in the core overheating or melting. If such an event were to occur, there is a chance that radioactive fission products may be released to the environment. The potential radiation exposure of the population will be influenced by the amounts of various radionuclides released, by the meteorological conditions affecting the dispersion and deposition of the released radioactive material, by human and environmental factors, and by the effectiveness of any protective actions taken.

Protective actions are taken in order to (1) prevent so-called deterministic effects (hypothyroidism, for example) from high levels of radiation exposure, and (2) reduce the risk of stochastic effects (for example, thyroid cancer and benign nodules) from exposure to levels as low as reasonably achievable. However, during and shortly after the onset of an accident, there are great uncertainties concerning the levels and extent of potential radiation exposure of the population. In order to protect people close to the reactor effectively from deterministic effects, precautionary protective actions are usually planned to be implemented for populations in the immediate vicinity, that is up to about 5 km, based on plant conditions and before any potential release occurs. If a release has begun, measurements can be taken that can help to limit the estimated risk to the population; nevertheless, it is extremely difficult to predict accurately the time variation and length of the release from the damaged reactor, its dispersion and subsequent doses to the population at greater distances. After the release stops, measurements of deposition and concentrations of radioactive materials in foodstuffs can be taken to confirm accurately the basis for any future protective actions.

In order to be able to respond rapidly, consistently and appropriately, national authorities will have an emergency plan. This plan will take into account the potential magnitude and likelihood of releases, and distances from reactors. It sets out responsibilities and authorities for decision-making and for protective actions, and also lays down so-called intervention levels for the various protective actions, which can be used in preparing detailed emergency response plans. The various protective actions for which detailed plans are made include sheltering and evacuation, which can reduce both the external and internal radiation exposure of the population, food and agricultural countermeasures to restrict ingestion of radioactive material, as well as stable iodine prophylaxis.

Isotopes of iodine (^{131}I, ^{132}I, including that arising from the decay of tellurium-132 (^{132}Te), ^{133}I; see Annex 1 for table of half-lives) are likely to be important components of the release from a severe accident. Radioactive iodines can give rise to both external exposure and internal exposure (from inhalation and ingestion). Stable iodine prophylaxis is a protective action for which preparedness arrangements can be made as part of the overall emergency response plan, and that can protect specifically against internal exposure from inhalation and ingestion of radioiodines.

It should be noted that the term “iodine prophylaxis” refers to the blocking of the uptake of radioiodine after nuclear accidents and not to the correction of dietary iodine deficiency.

The decision to plan for short-term prophylaxis against radioactive iodine should not be influenced by dietary iodine status. Dietary iodine deficiency increases the uptake of radioactive iodine in the thyroid. However, a normal iodine status would not reduce the need for prompt stable iodine prophylaxis in the event of a nuclear emergency. While dietary iodine supplementation in iodine-deficient areas is important in its own right, it does not eliminate the need to plan for stable iodine prophylaxis.

2. Radiation risk from radioactive iodine

2.1 Exposure to radioactive iodine

The radioactive isotopes of iodine, along with other radionuclides, give rise to external radiation exposure from radioactive material present in a radioactive cloud, deposited on the ground and on skin and clothing. In the case of the radioactive isotopes of iodine, a major concern is the internal radiation exposure following incorporation and uptake in the thyroid. This will occur through inhalation of contaminated air and ingestion of contaminated food and drink.

Absorption through the skin is a possible route, but negligible in comparison with inhalation.

2.2 Deterministic and stochastic effects

Deterministic effects from thyroid exposure are hypothyroidism and acute thyroiditis. Stochastic effects from thyroid exposure are thyroid cancer and benign thyroid nodules.

The selective and rapid concentration and storage of radioactive iodine in the thyroid gland results in internal radiation exposure of the thyroid, which may lead to an increased risk of thyroid cancer and benign nodules and, at high doses, hypothyroidism. These risks can be reduced or even prevented by proper implementation of stable iodine prophylaxis.

Hypothyroidism is caused by a radiation dose of the order of more than several Gy to the thyroid. A dose that large could, in practice, be incurred through inhalation only near the point of the accidental release. Because exposures from other radionuclides are also likely to be large in such cases, plans will usually include options to evacuate and/or shelter the population, and stable iodine can be a useful adjunct to these actions.

In regions where only the likelihood of stochastic effects is a cause for concern, stable iodine prophylaxis should be considered for sensitive population groups if potential exposure to radioactive iodine by inhalation or exposure by ingestion is expected to approach the reference levels given in Table 1, and cannot be prevented by sheltering or food and milk control. In severe accidents such situations may occur in areas quite far from the accident site.

Intake through ingestion of contaminated food, particularly milk, begins after deposition and transfer to the food chain. In the absence of any countermeasures, ingestion is likely to be the main route of internal radiation exposure to radioactive iodine. The exposure is likely to continue for a longer period, cover a wider area and affect a larger population than exposure by inhalation.

2.3 Experience from the Chernobyl accident

Evidence of a marked excess of thyroid cancer in children exposed to the fallout from the Chernobyl accident has been established *(1–10)*. In the most affected area in Belarus, the yearly incidence has risen close to 100 per million children, which is more than 100-fold compared to the situation before the accident. It is now generally accepted that this excess has resulted from exposure to the radioactive iodine released in the accident. The largest part of the dose to the thyroid was caused by ^{131}I although the shorter lived isotopes of iodine and ^{132}Te may have contributed significantly to the inhalation dose in some instances.

Table 1. Reference levels for different population groups for consideration in planning stable iodine prophylaxis[a]

Population group	Exposure pathways to be considered	Reference levels
Neonates, infants, children, adolescents to 18 years and pregnant and lactating women	Inhalation (and ingestion[b])	10 mGy[c] avertable dose to the thyroid
Adults under 40	Inhalation	100 mGy[c] avertable dose to the thyroid
Adults over 40 years	Inhalation	5 Gy[d] projected dose to the thyroid

Notes
[a]These idealized levels do not take into account the practicalities involved in planning to respond to an accident involving many radionuclides in unknown quantities in real time. For this reason, a generic intervention level of 100 mGy has been specified in the Basic Safety Standards. Nevertheless, this does not preclude the need to consider the practicality of planning to implement iodine prophylaxis for specific age groups.
[b]Ingestion of milk by infants where alternative supplies cannot be made available.
[c]Adherence to these values would ensure that doses for all age groups would be well below the threshold for deterministic effects.
[d]Intervention for this group is undertaken to ensure prevention of deterministic effects in the thyroid. 5Gy is the recommended limit for deterministic effects given in the Basic Safety Standards.

Following the Chernobyl accident there were several thousands of children who accumulated a dose to the thyroid of several Gy.

Nevertheless, most of the children that have developed thyroid cancer were exposed to an estimated dose to the thyroid of less than 300 mGy *(8)*. There has been an excess thyroid cancer incidence even in areas where the mean dose to the thyroid in children was estimated at 50–100 mGy *(9)*. The increase in incidence has been documented up to 500 km from the accident site. This is understandable in terms of the wide area affected by radioiodine and therefore the large number of children exposed.

The Chernobyl accident has thus demonstrated that significant doses from radioactive iodine can occur hundreds of kilometres from the site, beyond emergency planning zones. A sharp distinction in the requirements for stable iodine prophylaxis based on distance from the accident site cannot be made. For example, few regions in Europe are situated so far from a nuclear reactor as to preclude any potential need for stable iodine prophylaxis against inhaled or ingested radioactive iodine.

Another important insight gained from the Chernobyl accident concerns the side effects from stable iodine. In Poland stable iodine, as single doses, was given to 10 million children *(11)*. No serious side effects were seen, though gastrointestinal effects and minor skin rash were reported. Of newborn infants receiving 30 mg potassium iodide in their first two days of life, 0.37% (12 infants) showed a transient increase in serum thyroid stimulating hormone (TSH), combined with a decrease in serum free thyroxine (T4). This transient thyroid inhibition has had no known consequences to date. Seven million adults took stable iodine although it had not been recommended. Among these, only two severe adverse reactions were seen, both in persons with known iodine allergy. In summary, the incidence of severe side effects from a single dose of iodine was less than 1 in 10 million in children and less than 1 in a million in adults.

2.4 Estimates of cancer risk

Risk estimates for thyroid cancer attributable to radiation exposure have been made for populations exposed to external irradiation. According to the National Council on Radiation Protection (NCRP) *(12)*, the excess absolute risk (EAR) is 2.5×10^{-4}/Gy per year for persons exposed under the age of 18. For adults, the risk per year is taken as half this value.

The lifetime risk for adults would be 1/4 of the risk for children, because of the smaller number of years at risk.

The most current estimate, based upon a pooled analysis including five cohort studies, gives an EAR of 4.4×10^{-4}/Gy per year for persons exposed before the age of 15 *(13)*. The study indicated the relative risk to be heavily dependent upon age at exposure, younger children being at significantly higher risk than older ones. From the Lifespan Study of atomic bomb survivors in Hiroshima and Nagasaki it is known that little risk is indicated after the age of 20 and virtually none for exposure after the age of 40 *(14)*.

While internal exposure to radioactive iodine in medical use has not been shown to cause thyroid cancer in adults, the clinical experience in the case of young children is very limited. The experience from the Chernobyl accident shows the risk to be real. While the thyroid sensitivity in adults to both external radiation and ^{131}I seems to be minimal, or even absent in the elderly, sensitivity in young children is high.

According to a recent dose–response analysis based on combined data from Belarus, Ukraine and the Russian Federation, the three countries most affected by the Chernobyl accident, the risk for those aged 0–15 at exposure was 2.3×10^{-4}/Gy per year with 95% confidence intervals that overlap those of the pooled analysis (13) *(9)*. More recently an analysis of time trends in thyroid cancer incidence in Gomel in Belarus *(10)* concludes that risk estimates from external exposure are consistent with risk estimates from Gomel assuming that the increase in excess cases reaches a plateau soon. If this risk persists unchanged for 40–50 years, the lifetime risk of cancer would be about 1%/Gy.

For public health purposes in emergency planning and response, it is, therefore, prudent to assume equivalence of carcinogenic effect between X-rays and radiation from ^{131}I.

Radiation-induced thyroid cancer is not a trivial disease, although it has a very low mortality if properly treated. It causes significant morbidity and the treatment is lifelong, putting a considerable burden on the health care system.

3. Stable iodine prophylaxis as a protective measure

3.1 The rationale for administration of stable iodine

Stable iodine administered before, or promptly after, intake of radioactive iodine can block or reduce the accumulation of radioactive iodine in the thyroid.

Intake of radioactive iodine by inhalation begins when the radioactive cloud arrives at a location and continues during the passage of the cloud. Action to implement stable iodine prophylaxis, and thereby reduce the dose to the thyroid, will be required promptly. The decision will most probably have to be made in a situation when reliable data for calculating the potential dose to the thyroid are not available.

Stable iodine could also be used as prophylaxis against ingested radioactive iodine from contaminated food. However, because the risk of exposure from ingestion of iodine will remain for a longer time, iodine prophylaxis will also be required for a longer period of time, leading to a need for repeated doses. The side effect rate from multiple doses would be higher, but the frequency is not known. It is probably low in children but may be significant in adults, especially in areas with dietary iodine deficiency.

Exposure by ingestion can also be considerably reduced by agricultural countermeasures such as removing grazing animals from contaminated pasture or by the imposition of appropriate controls on agricultural products. In general, food controls would be easier to implement and more effective in the long term in reducing the collective dose than stable iodine prophylaxis. Therefore, agricultural and food control measures are preferable to repeated doses of stable iodine.

3.2 Side effects from stable iodine: general considerations

Thyroidal side effects may result from stable iodine administration, especially in iodine deficient regions. There is an increased risk in connection with thyroid disorders, such as auto-immune thyroiditis, Graves' disease and nodular goitre. Such disorders are common in the adult population and in the elderly but relatively rare in children. The risk of thyroid blocking in the newborn deserves special attention and is treated in more detail below.

Side effects in other parts of the body, such as gastrointestinal effects or hypersensitivity reactions, may occur but are generally mild and can be considered of minor importance. Dermatitis herpetiformis and hypocomplementaemic vasculitis entail an increased risk of severe hypersensitivity reactions.

The Polish experience, cited above in section 2.3, showed the risk of severe side effects from single doses of stable iodine to be minimal (less than 1 in 10 million in children and less than 1 in a million in adults). However, for repeated doses, there is no direct human experience that can be used for reliable numerical estimation of side effects.

3.3 Consideration of exposed population groups

Exposed population groups differ markedly in their risk of radiation induced thyroid cancer from a given radiation dose. Neonates, infants and small children are the most sensitive groups. The risk of side effects from stable iodine prophylaxis is also different, albeit generally small in the light of the latest experience. Because of these differences it is important to consider potentially exposed population groups separately when deciding on plans for stable iodine prophylaxis.

In general, the potential benefit of iodine prophylaxis will be greater in the young, firstly because the small size of the thyroid means that a higher radiation dose is accumulated per unit intake of radioactive iodine. Secondly, the thyroid of the fetus, neonate and young infant has a higher yearly thyroid cancer risk per unit dose than the thyroid of an adult and, thirdly, the young will have a longer time span for the expression of the increased cancer risk.

Individual radiation doses will also differ markedly within any exposed group. The intake of radioactive iodine through inhalation will be influenced by breathing rates and intake through ingestion will be influenced by dietary habits.

In the following, the risks from radiation exposure and the risks from stable iodine prophylaxis, respectively, are examined in more detail for the various population groups.

Pregnant women

During pregnancy, the maternal thyroid gland is stimulated, especially during the first trimester. The fraction of radioactive iodine taken up by the thyroid is increased as compared to other adults. Thus, there is a greater need to protect the thyroid gland of the pregnant woman.

During the second and third trimesters, the thyroid gland of the developing fetus takes up and stores iodine in increasing amounts. Iodine passes readily across the placenta, and thus, after the first trimester, the fetal thyroid gland can be exposed to radioactive iodine through the placenta, but it can also be protected by stable iodine taken by the mother. However, the risk of blocking the fetal thyroid function by a prolonged overload of stable iodine must be kept in mind, especially in areas with inherent dietary iodine deficiency.

While there are physiological differences between the trimesters, outlined above, there is no need for a different policy of intervention, which would create substantial problems in practice. Throughout pregnancy, the number of stable iodine doses should be kept to the minimum needed to provide adequate protection against inhaled radioactive iodine. No negative consequences are to be expected after one or two doses of stable iodine. However, especially in areas with dietary iodine deficiency, prolonged dosage could lead to maternal and/or fetal thyroid blockage, with possible consequences for fetal development. It is important, therefore, that this be avoided. To protect against ingestion of radioactive iodine, which would imply repeated doses of stable iodine, appropriate food control measures such as the provision of uncontaminated milk must be given priority. If stable iodine is given late in pregnancy, there is a need to monitor the newborn for thyroid function, but this would be met by routine screening programmes already in place in most countries. Pregnant women with active hyperthyroidism must not take stable iodine because of the risk of fetal thyroid blockage.

Neonates

Newborn infants are quite likely the critical group of concern when deciding on the implementation of stable iodine prophylaxis. In the first few days of life they are at special risk both of exposure from radioactive iodine and blocking of thyroid function by an overload of stable iodine.

After birth, there is a dramatic increase in thyroid activity, lasting only a couple of days. The fraction of radioactive iodine intake that will be incorporated into the thyroid at this critical stage can be fourfold greater than for all other age groups *(15)*. On the other hand, during this period the thyroid is especially sensitive to the functional blocking caused by an overload of stable iodine. The most critical period for developing thyroid blockage lasts for less than a week, even in the premature. Even transient hypothyroidism during the critical period of brain development can result in loss of intellectual capacity *(16)*. The potential for harmful influence on neurointellectual development, however, was not confirmed in the Polish study referred to in section 2.3.

When indicated, stable iodine in the form of potassium iodide (KI) will be promptly given to all neonates. The dosage is critical. A single administration of 12.5 mg iodine (16 mg KI) should not be exceeded. If stable iodine is given, close follow-up is essential.

KI solution should be readily available in maternity hospitals. This will enable prompt and exact dosage to the critical group of the newborn still on the ward. A few days later the sensitivity for blockage of thyroid function will have decreased and dosage may be performed at home, by dividing, crushing and suspending tablets in milk or water. In infants who have been administered stable iodine in the first weeks of life, TSH levels and, if indicated, T_4 levels will be monitored and appropriate replacement therapy given.

Infants, children and adolescents (1 month to 18 years)

These groups are at high risk from exposure to radioactive iodine but at very low risk from stable iodine. The dose to the thyroid from radioactive iodine in a given situation will be higher in this group than in adults because of the smaller size of the gland, which is only partly compensated for by a smaller breathing volume. The highest dose

from inhalation, up to threefold as compared to adults, will be in children around three years old. The dose from ingestion may be several times higher compared to adults, because of the generally high consumption of milk in relation to thyroid mass in this group.
When intervention is decided upon, based on the emergency plans and predetermined operational intervention levels, stable iodine should promptly be given to all children. If intake of radioactive iodine through inhalation is prolonged, the recommended single stable iodine dose (cf. Table 2) will be repeated daily. This would most probably cause no harm. However, in children showing skin reaction to the first dosage, the stable iodine administration should not be given repeated doses.

Table 2. Recommended single dosage of stable iodine according to age group

Age group	Mass of iodine mg	Mass of KI mg	Mass of KIO_3 mg	Fraction of 100 mg tablet
Adults and adolescents (over 12 years)	100	130	170	1
Children (3–12 years)	50	65	85	1/2
Infants (1 month to 3 years)	25	32	42	1/4
Neonates (birth to 1 month)	12.5	16	21	1/8

In general, appropriate control of foodstuffs is to be given priority as the countermeasure against ingestion of radioactive iodine. In the exceptional case that this is not possible, or when it would lead to deficiency of essential nutrients such as milk, prophylaxis with daily doses of stable iodine can be continued for a few days, or even weeks, in this group, as necessary.

Lactating mothers

Iodine is actively transported to the milk. As much as 1/4 of the iodine taken by the mother may be secreted in the milk within 24 h *(17)*. An excess of stable iodine can block the transport to a certain extent. However, if the infant is administered stable iodine, it will be protected from radioactive iodine in the milk for the next day. Therefore, stable iodine prophylaxis for lactating mothers can be decided upon by the same criteria as for other young adults, to protect the woman herself. Repeated dosage is to be avoided.

Adults under 40 years

In young adults, the risk of radiation induced thyroid cancer is low *(14)*. On the other hand, the risk of serious side effects from a single dose of stable iodine is also low. Stable iodine as a single dose can be given to this group if intervention is decided upon. The dose criteria for intervention will in principle be significantly higher than for children. It will be important that contraindications (known iodine allergy, present or past thyroid disease of any kind, dermatitis herpetiformis, and hypocomplementaemic vasculitis) be taken into consideration.

Repeated administration of stable iodine for protection against ingested radioactive iodine is not indicated in this group, as the risk of side effects will be increased. Appropriate control of food may also be easier for adults than for children. Adults could, for example, completely abstain from drinking milk during the contamination period, without fear of nutritional effects.

Adults over 40 years

The risk of radiation induced thyroid cancer in this group is probably extremely low and may even be zero *(14)*. The risk of side effects from stable iodine increases with increasing age as the incidence of thyroid diseases is higher. Stable iodine prophylaxis is not indicated for this group, unless doses to the thyroid from inhalation rise to levels threatening thyroid function, that is of the order of about 5 Gy. Such radiation doses will not occur far away from an accident site (cf. section 2.2).

4. Implementation of stable iodine prophylaxis

4.1 Intervention levels

According to the basic principles of radiological protection, intervention to protect the public should be undertaken if serious deterministic effects are projected or if there is a high individual risk of stochastic effects; and protective actions should achieve more good than harm and reduce the risk of stochastic effects to as low as reasonably achievable.
The decision to initiate stable iodine prophylaxis should generally be made on the basis of predetermined conditions specified in the emergency plans. These conditions can include the accident classification and levels of measurable quantities that will trigger response. These conditions and levels are precalculated, in part on the basis of so-called intervention levels, which in turn are specified in terms of avertable dose. The avertable dose is defined as the dose to be saved by the particular protective action; in this case, the difference between the dose to be expected with stable iodine prophylaxis and that to be expected without it. In the International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources *(18)*, a generic intervention level of 100 mGy avertable dose is recommended for all age groups.

Notwithstanding the generic recommendation, it is appropriate to consider the differing risks for different age groups when developing detailed emergency plans, and also the possibility of differential administration of stable iodine prophylaxis. In this way, the greater need of children for stable iodine and the greater risk of side effects in the elderly, can be separately catered for. Emergency plans also need to complement plans for evacuation, sheltering and food control, and take into account doses to any workers involved in distribution.

As side effects from short-term stable iodine prophylaxis are now known to be minimal, the decision to plan for prophylaxis will depend mainly on the estimated social and economic costs. Provided that predistribution of stable iodine to strategic sites has taken place and iodine tablets are readily accessible, the costs will be low. Nevertheless, consideration will need to be given to the psychosocial consequences of iodine prophylaxis, both in terms of the reassurance it may provide and any possible anxiety it may create among the population.

4.2 Balance between risk and benefit of taking stable iodine

The lifetime cancer risk for exposed children can be taken to be 1%/Gy (see section 2.4) and the risk of severe side effects from a single administration of stable iodine to be 10^{-7}. Accordingly, a risk equals benefit analysis (ignoring other factors) in averting doses as small as 0.01 mGy. In practice, this means that the risk of severe side effects can be ignored when deciding on the intervention level. Minor side effects from stable iodine prophylaxis, such as skin rash or gastrointestinal complaint, constitute no major problem.

On assuming a severe accident and applying the risk estimates for children cited in section 2.4 and the generic intervention level of 100 mGy, without regard to age group, the incidence of thyroid cancer among those most exposed might be of the order of 20–50 per million children per year. This is to be seen against the background of spontaneous childhood thyroid cancer of about 1 case per million children per year. The corresponding lifetime risk would be 0.1–0.3% for all children and even more for small children of the most sensitive age. On the other hand, applying an age-specific intervention level of 10 mGy radiation dose to the thyroid, the incidence of thyroid cancer among those most exposed might be some 2–5 extra cases per million children per year, still a several fold increase compared to the generally encountered background incidence. The corresponding individual lifetime risk would be of the order of $1–3\times10^{-4}$.

In view of the established relatively high risk of thyroid cancer among those exposed in childhood, planning for stable iodine prophylaxis for children should ideally be considered at 1/10th of the generic intervention level, that is at 10 mGy avertable dose to the thyroid. This level is also appropriate for pregnant women.

Even if an avertable dose were grossly overestimated in a real emergency, no significant health hazard would result from stable iodine administration.

It has not been possible to make a corresponding risk–benefit analysis for adults, as the carcinogenic effect from ^{131}I in adults has not so far been confirmed. For young adults, however, in the light of the low frequency of severe side effects (10^{-6}) from single doses of stable iodine, prudence argues in favour of applying the generic intervention level given in the Basic Safety Standards.

For adults over 40, the risk of radiation-induced thyroid cancer is presumed to be close to zero. For this group, the implementation of stable iodine prophylaxis is determined by the need to ensure prevention of deterministic effects. This is guaranteed by an action level of 5 Gy projected dose to the thyroid (but see section 5).

Table 1 summarizes the reference levels for different population groups for consideration in planning stable iodine prophylaxis.

5. Considerations in planning the use of iodine prophylaxis in conjunction with other countermeasures

In emergencies involving a release to the environment of radioactive iodine there is a need for an early warning and rapid response so that measures that prevent or mitigate exposure can be implemented. Such measures include evacuation, sheltering and food controls as well as iodine prophylaxis. The optimum response will often involve the combined use of these countermeasures.

It should be noted that while the other countermeasures protect against most radionuclides and external exposure, iodine prophylaxis protects only against inhaled or ingested radioiodine.

5.1 Evacuation

Evacuation means temporarily moving people out of the area predicted to be affected by the radioactive release. Evacuation is most effective when implemented before the passage of the radioactive cloud. Precautionary evacuation will pre-empt the need for stable iodine administration, but instructions to take iodine tablets when pre-distributed should be considered in planning.

Evacuation will be decided upon primarily on the basis of plant conditions and meteorological data. However, plans should take account of the fact that persons to be evacuated may have been exposed to the radioactive cloud.

5.2 Sheltering

Advising the population to stay indoors is a relatively simple protective measure in the early phase of an accident. The decision to implement sheltering will be considered in nuclear emergency planning as a means of protection against external radiation as well as against inhalation of all radionuclides.
Inhalation of radioactive iodine from a passing cloud will be reduced to some degree by sheltering indoors with closed windows and any forced ventilation shut off, but sheltering is not completely effective in avoiding inhalation doses. Realistic dose estimates need to be taken into account in considering plans for the implementation of stable iodine prophylaxis.

It is important that planning for the simultaneous implementation of stable iodine prophylaxis be seriously considered as a supplement to sheltering plans where the expected avertable inhalation dose to the thyroid approaches those in Table 1, and for those accidents where radioactive iodine is a major component of the release.

5.3 Food control

The principal protective measures against internal exposure through ingestion are firstly, agricultural countermeasures (such as putting grazing animals on stored feed) followed by the banning of potentially contaminated foodstuffs or locally produced agricultural products. For this route of exposure or pathway, food control is generally preferable to the use of stable iodine prophylaxis.

However, withholding milk from infants and young children will have disadvantages and, in some circumstances, it may be foreseen that the rapid distribution of uncontaminated milk to infants or transfer of animals to stored feed cannot be arranged or planned. Therefore, in considering plans for stable iodine prophylaxis for infants and young children, it is important that this issue be taken into account.

For other population groups, the removal of milk from the diet for several days is an inconvenience but this is no argument to plan for iodine prophylaxis as an alternative to food control or agricultural countermeasures.

6. Logistics of stable iodine prophylaxis

6.1 Chemical form

Stable iodine can be used either as potassium iodide (KI) or potassium iodate (KIO_3). KI is the preferred alternative, since KIO_3 has the disadvantage of being a stronger intestinal irritant *(19)*.

There is no decisive difference in shelf life between KIO_3 and KI. If storage conditions are adequate, the expected shelf life of the tablets is at least 5 years. After 5 years the iodine content may be checked and the shelf life extended, if indicated.

6.2 Formulation, storage and packaging

Stable iodine can be given in either doubly scored tablet or liquid form. Tablets have the advantage of easy storage and distribution, including predistribution. Also, stable iodine is likely to cause less gastrointestinal irritation if administered in tablet form. Tablets can be crushed and mixed with fruit juice, jam, milk or similar substance.

Tablets should be stored protected from air, heat, light and moisture. Age-dependent dosage and contraindications should be on the labelling.

Tablets packed in a hermetic alufoil and kept in a dry and cool place preserve fully their iodine content for 5 years *(20)*.

6.3 Availability, predistribution and distribution

As there is only limited time for implementation of prophylaxis, prompt availability of the tablets to individuals has to be ensured if they are to be at their most effective. In the vicinity of nuclear reactors, predistribution to households should be seriously considered, taking into account plans for evacuation and sheltering, with provision for storage in places that can be controlled by the responsible authorities. Clear instructions should be issued with the tablets, and public awareness of the procedures should be monitored on a regular basis. Medical personnel likely to be consulted by the public should be provided with more detailed information.
At greater distances from the site of release there is likely to be more time for decision-making. If predistribution to households is not considered feasible, stocks of stable iodine should be stored strategically at points that may include schools, hospitals, pharmacies, fire stations, police stations and civil defence centres. Widespread storage may be warranted at considerable distances from the potential accident site. Storage should preferably be at places where proper stock control is standard practice. Planning should consider the use of redundant distribution areas to minimize delays in implementing stable iodine prophylaxis. Due consideration should also be given to whether the benefits of stable iodine distribution outweigh the disadvantages associated with any additional exposure of responsible emergency personnel.

National authorities are advised that, because of the benefits of stable iodine prophylaxis and the generally minimal risks of side effects, voluntary purchase of iodine tablets by the general public should be allowed. However, within the framework of the overall nuclear emergency plan, the responsibility for distribution of stable iodine and instructing the public on how to use it should still be clearly assigned to the appropriate authorities.

6.4 Dosage and contraindications

For adequate suppression, the dosage scheme given in Table 2, which is based on a single dose for adults of 100 mg of iodine, is recommended.

The tablet divisions indicated in Table 2 are easy to achieve with a tablet stamped by a cross, except that the exact dosage of 1/8 tablet required for neonates is difficult to ensure. However, for neonates over 1 week of age living at home, an approximate division would be satisfactory. The most sensitive group of the newborn, those less than 1 week old, should preferably have a more exact dosage. This can be achieved with KI solution freshly prepared from crystals. It is, therefore, recommended that maternity wards keep KI in storage in crystal form.

As an alternative, tablets containing 50 mg of iodine (65 mg KI or 85 mg KIO_3) can be used, correspondingly doubling the tablet dosage indicated in Table 2. It is recognized that some iodine tablets are too small to subdivide effectively and it is recommended that tablets of sufficient size be manufactured.
The contraindications for use of stable iodine are:

- past or present thyroid disease (e.g. active hyperthyroidism)
- known iodine hypersensitivity
- dermatitis herpetiformis
- hypocomplementaemic vasculitis.

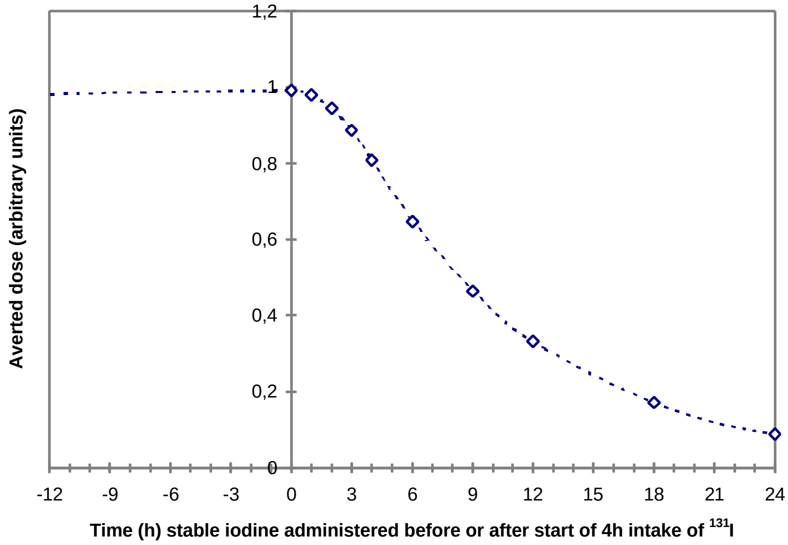
These should be clearly stated on the labelling.

6.5 Timing of administration and duration of prophylaxis

To obtain full effectiveness of stable iodine for thyroidal blocking requires that it be administered shortly before exposure or as soon after as possible. However, iodine uptake is blocked by 50% even after a delay of several hours. Fig. 1 shows the effectiveness of thyroid blocking achieved by administering stable iodine at different times before or after a 4-h exposure to radioiodine.

To protect against inhaled radioactive iodine, a single dose of stable iodine would generally be sufficient, as it gives adequate protection for one day. This may well be enough to protect from inhaled radioactive iodine present in a passing cloud. In the event of a prolonged release, however, repeated doses might be indicated.

Fig. 1. Averted dose as a function of time stable iodine is administered relative to a 4-h intake of ^{131}I for different dietary iodine intakes



In some circumstances stable iodine administration may also be practical in limiting the dose to the thyroid from ingested radioactive iodine, especially to children via the milk pathway where alternative sources cannot be found. In that case, a daily dose of stable iodine may be given for the time period needed to those children who show no adverse reaction. Repeated administrations should not be given to neonates, or to pregnant or lactating women (see section 3.2).

Due consideration should be given, in preparing emergency plans, to mitigating any adverse psychosocial reactions to the implementation of iodine prophylaxis. To avoid public concern, distribution and instructions to different age groups must be orderly and consistent. There are advantages in consulting with neighbouring countries with regard to their national policy in order to avoid discrepancies of approach, especially where reactors are close to national borders.

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Annex 1

HALF-LIVES OF THE IMPORTANT RADIOISOTOPES RELATED TO RADIOACTIVE IODINE FOUND IN FISSION PRODUCTS

Nuclide	Half-life
^{131}I	8.04 d
^{132}I	2.3 h
^{133}I	20.8 h
^{135}I	6.61 h
^{132}Te	3.26 d

Annex 2

GLOSSARY OF TERMS AND ACRONYMS

Terms

Accident	Any unintended event, including operating errors, equipment failures or other mishaps, the consequences or potential consequences of which are not negligible from the point of view of protection or safety.
Autoimmune thyroiditis	A chronic inflammatory disease of the thyroid gland with anti-thyroid antibodies present in the blood (Hashimoto's thyroiditis). Often leads to hypothyroidism.
Avertable dose	The dose to be saved by a protective action; that is, the difference between the dose to be expected with the protective action and that to be expected without it.
Basic safety standards	A comprehensive set of standards for radiological protection and the safety of radiation sources, agreed between various international organizations, including WHO and IAEA, for international application.
Dermatitis herpetiformis	A chronic skin manifestation of gluten sensitivity (coeliac disease) with clusters of itching papules, vesicles and crusts, mostly on the knees, elbows or buttocks.
Deterministic effect	A radiation effect for which generally a threshold level of dose exists above which the severity of the effect is greater for a higher dose (see also stochastic effect).
Dosage	Schedule for administration of a medical preparation (e.g. potassium iodide) in a prescribed amount.

Dose	A measure of the radiation received or ‘absorbed’ by a target. the quantities termed absorbed dose, organ dose, equivalent dose, effective dose, committed equivalent dose or committed effective dose are used, depending on the context. the modifying terms are often omitted when they are not necessary for defining the quantity of interest. *In medicine:* identical to dosage (see above). To avoid confusion in this document, the term dose has been reserved for use in the context described above and the term dosage has been used to indicate the medical context.
Emergency plan	A set of procedures to be implemented in the event of an accident.
Excess absolute risk (EAR)	The excess number of cases induced by one unit exposure, in addition to the spontaneous number of cases. ear is usually expressed as number of cases per year per 10 000 persons exposed to a dose of 1 Gy.
Exposure	The act or condition of being subject to irradiation. exposure can be either external exposure (irradiation by sources outside the body) or internal exposure (irradiation by sources inside the body). exposure can be classified as either normal exposure or potential exposure; either occupational, medical or public exposure; and, in intervention situations, either emergency exposure or chronic exposure. the term exposure is also used in radiation dosimetry to express the amount of ionization produced in air by ionizing radiation.
Formulation	The composition, both in terms of chemical form and quantity, for a pharmaceutical product (e.g. potassium iodide or iodate in

	milligrams and quantities of other ingredients of a tablet).
Generic intervention level (GIL)	A predetermined intervention level specified for a particular intervention. For example, the GIL for distribution of stable iodine recommended in the Basic Safety Standards is 100 mGy. GILs are primarily intended for planning purposes.
Graves' disease	A syndrome characterized by diffuse goitre, excessive functional activity of the thyroid gland (hyperthyroidism) and often associated with protrusion of the eyes (exophthalmos).
Hyperthyroidism	Excessive functional activity of the thyroid gland.
Hypocomplementaemic vasculitis	Hypocomplementaemic urticarial vasculitis syndrome (HUVS), a rare, severe, autoimmune disorder related to systemic lupus erythematosus. Symptoms caused by inflammation in blood vessels may be limited to the skin (recurrent urticaria) or involve multiple organs such as joints, kidneys, and lungs. The level of complements in the blood is depressed and complement antibodies are present. Severe allergic reaction to iodine has been described in these patients.
Hypothyroidism	Deficiency of thyroid activity.
Intervention	Any action intended to reduce or avert exposure or the likelihood of exposure to sources which are not part of a controlled practice or which are out of control as a consequence of the accident.
Intervention level	The level of avertable dose at which a specific protective action or remedial action is taken in the event of emergency exposure or chronic exposure.

Ionizing radiation	For the purposes of radiation protection, radiation capable of producing ion pairs in biological material(s).
KI and KIO_3	Potassium iodide and potassium iodate, respectively, the two chemical forms of stable iodine recommended for protection against exposure to radioiodine.
Predistribution	Distribution to and supervised storage at local centres, such as police stations, hospitals, schools, fire stations, from where distribution to individuals can readily be made at short notice.
Reference level	Action level, intervention level, investigation level or recording level. Such levels may be established for any of the quantities determined in the practice of radiation protection.
Stable iodine	Non-radioactive isotope of iodine.
Stochastic effect	Radiation effects, generally occurring without a threshold level of dose, whose probability is proportional to the dose and whose severity is independent of the dose (see also deterministic effect).
T_4	Thyroxine, the hormone secreted by the thyroid gland.
Free T_4	The metabolically active form of thyroxine, circulating in the blood without being bound to a protein.
TSH	Thyroid-stimulating hormone, a hypophyseal hormone involved in regulating the thyroid function. An increased value indicates a latent or manifest deficiency in thyroid function. Used in screening of the newborn for congenital hypothyroidism.

Acronyms

FAO	Food and Agricultural Organization (a specialized United Nations agency)
IAEA	International Atomic Energy Agency (a specialized United Nations agency)
ILO	International Labour Organisation (a specialized United Nations agency)
NCRP	National Commission on Radiological Protection (a United States agency)
OECD/NEA	Organisation for Economic and Cultural Development/ Nuclear Energy Agency
PAHO	Pan American Health Organization (part of the Organization of American States)
WHO	World Health Organization (a specialized United Nations agency)

Reference 4

Between stable iodine prophylaxis and evacuation

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Introduction

Iodine prophylaxis is a countermeasure that can protect the thyroid against irradiation in the event of exposure to radioactive iodine that might result from an accident to a nuclear power plant. In these circumstances radio-iodines are an important potential hazard, especially to children as the Chernobyl accident has so clearly demonstrated. Some 2000 cases of thyroid cancer in those who were children at the time of the accident have been confirmed as resulting from exposure to radio iodine.

Why is iodine so important in a nuclear accident?

Iodine is a very volatile element and so at reactor operating temperatures is a vapour and diffuses rapidly in the fuel pin and release starts as soon as the pin containment is breached. If there is no secondary containment and the primary containment is breached, release to the environment is inevitable. The Chernobyl accident illustrated how far radio-iodine could travel after release. Excess cases of childhood thyroid cancer have been observed more than 500 km from the site of the accident.

Why are children so much more at risk than adults?

There are two reasons, the first is that the thyroid is a small gland, weighing about 1 gm at birth and 20 grm for the adult. The thyroid avidly absorbs and retains iodine once iodine has reached the blood. The radiation dose is the energy absorbed per unit mass of tissue and, therefore, the dose per decay of ^{131}I in the thyroid will be higher the younger the child.

The second reason is that the child's thyroid is much more sensitive per unit of dose, to the carcinogenic effects of ionising radiation, than that of the adult. This is probably is due to the biological function of the thyroid in controlling growth. normal thyroid cells have little capacity to divide further after adulthood is reached.

Although inhaling iodine from the cloud can be an important source of ^{131}I in an accident much larger populations are generally at risk from ingesting ^{131}I in milk.
Since the child and adult intakes of milk are roughly equal, children get much higher doses to the thyroid as well as being much more sensitive to the effects of the exposure.

How should we respond to a nuclear accident?

Of course a nuclear accident is about much more than protecting children from radio-iodine, but as iodine is almost always going to be present in fallout from an operating reactor, it represents a typical 'microcosm' embedded in the much larger problem that an accident such a Chernobyl poses.

There are three important factors to consider, namely,

- What are the important routes of exposure
- What are the important factors in the exposed populations
- What means do we have at our disposal to minimise such exposures

What are the important routes of exposure?

This depends on location in relation to the source of the exposure and certain behavioural characteristics. Close to the source (say within 5 km) inhalation could be a serious hazard but it lasts only while the released radioactivity is in the air. At greater distances (say >20 km) ingestion will be the greater threat, particularly where fresh milk produced locally is consumed, because radioactivity deposited on pastures can enter the food chain. This threat lasts for a few months (in the case of iodine but many tens of years for radio-caesium) but radioactive decay and weathering of the pasture reduces the level of fallout with time.

What are the important factors in the potentially exposed populations?

Age is the most important factor because of the size of the thyroid. Gender is also a factor because of pregnancy (foetal thyroid activity starts at about 3 months post fertilisation) and lactation status. (Females are also about 3 times more sensitive to the carcinogenic effects of radiation on the thyroid).

How can such exposures be minimised ?

There are five potential countermeasures that can be taken to reduce the exposure of populations to radio-iodines. They are as follows :

- Evacuation
- Sheltering
- Food controls
- Agricultural controls
- Stable Iodine Prophylaxis

Rationale for implementing countermeasures

The ICRP recommends that countermeasures should only be introduced if they carry a net benefit in terms of the dose they can avert. This means that it is not only the effectiveness in averting dose, but also the risks entailed in taking the countermeasure that need to be considered. Thus, in effect, a cost benefit analysis has to be performed in respect of each countermeasure.

Countermeasure	Benefits	Risks and costs
Evacuation	Immediate removal from the threat	Accidents, exposure during the process, social disruption, policing etc.
Sheltering	Reduced exposure to inhalation hazard	More-or-less risk and cost free but social implications if prolonged
Agricultural controls	Reduces amount of radio-iodine entering the food chain	Risk free but stored fodder required while cattle are off pasture
Food controls	Reduces uptake of radio-iodine by the thyroid from ingestion	Few risks but milk has to be thrown away and there are administrative costs in redistribution of supplies
Stable Iodine Prophylaxis	Complete blocking of radio-iodine uptake for about 2 days if given at the right time.	No risk to children, some adults and neonates are at or potentially at, risk. Tablets have to be made stored and distributed.

Table 1. Comparison of the benefits of countermeasures with their risks and costs.

Evacuation should, therefore, be used close to the source and preferably before the exposure starts, i.e. as a pre-emptive action. It is essential for high-risk groups. Sheltering is appropriate also close in, but is less effective but can be used in conjunction with other measures, such as stable iodine prophylaxis. It may be preferable to evacuation if there is a risk of exposure during the evacuation. Agricultural controls are a good measure at all distances to reduce ingested doses if sufficient stored fodder is available. This may not be the case at all times of the year. Food controls are an effective measure at all distances to reduce ingested doses. Stable iodine prophylaxis is a good short-term measure close to the source of the exposure. At greater distances it can also be used for children for a few days only, while other measures are put in place.

It has to be recognised that all these countermeasures affect people

All these actions apply to people and they should understand what is being done and why. Parents may be separated from their children, specific instructions apply such as "children should take tablets but not adults", some milk supplies are safe to drink, some are not, etc., are some of the issues that may arise and cause concern and anxiety, in themselves public health detriments. Thus, public education is an important aspect of an effective response to an accident. Ideally it should be ongoing and not wait until the accident happens.

What has been learned about the optimum response?

- That to protect public health from even just radioactive iodine in the event of an accident involves a complex web of factors to be considered. That optimum response will be "case specific", depending on many factors that cannot be anticipated. Therefore, each accident has to be considered in its particular context.
- That public health expertise is essential in developing the case specific response.
- That the necessary administrative structures to coordinate the response are in place, regularly reviewed and tested with exercises.
- That public education is essential if the psychosocial effects are to be minimised.

Are these lessons applied in practice?

In some countries the answer is YES, but in many it is NO. Adequate preparedness requires a substantial investment in planning, exercising, expertise and public education, in a highly co-ordinated way, between many players.

However, the cost of not investing in this infrastructure can be great. In Ukraine since Chernobyl the costs incurred by the accident were at least $5.6 billion between 1992 and 2000. The collective dose to 2055 is estimated to be 6,000 person.Sv. That is $93,000/ person.Sv. The full cost, including 1986 to 1992 and costs still to come, may well be closer to $200,000/personSv

Iodine will not be the only problem

As stated earlier protection from radioactive iodine is a 'microcosm' of a much greater issue. We have seen the results of exposure to iodine after Chernobyl. It is far from certain that we have seen all effects that are to come, or indeed, that are present now, in the exposed populations.

Summary

Responding to reactor accidents in order to protect public health is a complex matter involving many disciplines, but most notably, public health expertise. The most effective response will be that tailored to the specific circumstances of the accident, carried out within a well-coordinated framework that is subject to regular review and exercising. As the threat of exposure to fallout does not respect national borders an international coordinating role has to be fulfilled.

Reference 5

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Thyroid cancer in Belarus post-Chernobyl: Improved detection or increased incidence?

Summary

There is debate on whether the reported increase in the number of cases of childhood thyroid cancer in Belarus is real and attributable to radiation released following the Chernobyl nuclear accident, or rather an artefact due to incorrect histological diagnosis, more complete case reporting and mass screening of children after the accident. We have scrutinised the histological slides of 120 (75%) of the 160 cases reported among children aged up to 15 years to the Belarus tumour registry from 1986 to 1992 and examined time trends and geographical patterns in incidence and tumour characteristics. Incidence based on reported cases increased from 0.041 per 100.000 in 1986 to 2.548 in 1992. Carcinoma was confirmed in 94% of reviewed tumours. Except for one medullary carcinoma all histologies were of the papillary type. Most of the tumours had spread beyond the organ capsule and measured over 10 mm in diameter. There was a weak and statistically non-significant trend ($p = 0.19$) towards smaller tumours in the later years. The proportion of cases with lymphnode or distant metastasis remained unchanged. Incidence based on histologically confirmed cases was highest adjacent and to the west and north of Chernobyl, matching best estimates of iodine-131 contamination. Our data thus strongly suggest that the observed increase is real but more data are needed in order to assess the impact of mass screening and to clarify the possible association with radiation released at Chernobyl in 1986.

A pronounced increase in the number of thyroid cancer cases diagnosed among children in Belarus starting in 1988 and continuing through 1992 has been reported[1]. This has been attributed to radioiodines released following the accident which destroyed unit four of the Chernobyl reactor site on April 26, 1986, and which lead to radioactive contamination of large areas of the republic of Belarus[1,2]. Chernobyl is located in the Ukraine, near the Gomel district in the south-east of Belarus. The reported increase in childhood thyroid cancer occurred earlier than expected on the basis of much of the previous experience – in most studies of external radiation, a latent period of ten years or more has been documented[3]. On the other hand, reports of latent periods as short as 3 years can be found in the literature[4]. Patients with Graves' disease who were given therapeutic doses of iodine-131 have shown no increased risk of thyroid cancer[5]. It is therefore a matter of debate whether the excess observed among children in Belarus is real, and a number of alternative explanations have been put forward[6–8]. The increase could partly or entirely be attributable to false positive histological diagnoses or, conversely, be due to improved detection and more complete reporting of thyroid cancer cases because of increased awareness in the post-accident era. Furthermore, it has been argued that many of the reported cases could correspond to a dormant and thus clinically irrelevant type of carcinoma, occult papillary thyroid carcinoma, which has been described as a "normal finding" in autopsy studies[9].

We have re-examined the majority of histological slides and have assessed time trends and geographical patterns in tumour characteristics and incidence, in order to investigate the nature of this apparent epidemic of childhood thyroid cancer. Our objectives were to assess whether the excess could be artefactual due to (i) incorrect histological diagnoses, (ii) more complete case reporting in the post-Chernobyl era, or (iii) screening for thyroid tumours of large numbers of asymptomatic children in the years following the accident.

Material and methods

In Belarus, first medical contacts are with general policlinics, from which patients with suspected oncological conditions are referred to one of 12 specialized tumour clinics. These clinics, as well as all hospital departments throughout the country and the oncological centres in Minsk, are obliged by law to report all cases of neoplasms to a registry which was created in 1965 at the State Research Institute for Oncology and Medical Radiology in Lesnoj near Minsk (called in brief the Lesnoj Research Institute). Diagnoses are coded according to the 9th revision of the International Classification of Diseases (ICD-9)[10] and tumour stage is assessed using the TNM classification system[11]. Patient information includes name, age, sex, region (*oblast*) and district (*rayon*) of residence, date of diagnosis, reporting clinic and clinical follow-up data.
The histological slides of 120 children aged up to 15 years who were diagnosed as having thyroid cancer from 1986 to 1992 and who had undergone thyroid surgery were re-examined by a pathologist of the Lesnoj Research Institute (A.W.F.) and by two senior Swiss pathologists (B.E., C.R.). The International Classification of Thyroid Tumours[12] was used for histological grouping. Tumour size had been measured and invasion of neighbouring tissues and lymph nodes assessed immediately following surgery. Detailed procedures are described elsewhere[13].
Incidence rates based on population data obtained from the Belarus State Commission for Statistics, together with Poisson 95% confidence intervals, were calculated for the ten-year period preceding the accident at the Chernobyl nuclear power plant and for each year from 1986 to 1992. Comparison rates from Eastern Europe, Scandinavia and the United States were computed based on cancer registry data published by the World Health Organisation[14]. Incidence rates by *oblast* and, in some instances, by *rayon* were calculated for 1990 and 1991 combined and compared to patterns of radio-iodine contamination on May 10, 1986, as estimated by the Belarus Centre for Radiation Control and Environmental Radiation Surveillance on the basis of radionuclide emission and meteorological data.

Results

As shown in Table 1 the number of cases of childhood thyroid cancer reported to the registry increased from an average of 1 case per year during the ten-year period preceding the accident to 27 cases in 1990, 55 in 1991 and 66 in 1992. Incidence based on reported cases averaged 0.041 per 100,000 person-years (95% confidence intervals 0.019–0.078) during the decade preceding the accident, but had increased to 2.548 per 100,000 (1.94–3.28) by 1992; that is, a 62 times higher rate. The incidence of childhood thyroid cancer reported from Eastern European registries are comparable with the pre-accident rates from Belarus. The rates reported from the big Scandinavian and U.S. registries are still about 13 times below the rate reported from Belarus for 1992.
Among the 120 histological slides which were reviewed by outside pathologists carcinoma was confirmed in 113, corresponding to 94% of reviewed cases. Up to 1991, 93% of reported cases could be reviewed by our team, but this figure dropped to 41% in 1992 (Table 1). Overall, the 120 slides reviewed represent 75% of all 160 cases reported from 1986 to 1992. All cancers were of the papillary type except for one which was of the medullary type.
The characteristics of the 86 histologically confirmed cases diagnosed from 1986 to 1991 are shown in Table 2. Among these, all underwent thyroidectomy or hemithyroidectomy except for 1 patient who only had a node removed. Sixty percent of children were below 10 years of age at diagnosis. There was a slight female preponderance. The majority of cases were diagnosed in Gomel. Sixty-two percent of tumours had spread beyond the capsule, 65% had invaded cervical lymph nodes and (including follow-up information) 13% had spread to the lungs. On histological review, one case was reclassified from T2 to T4. The 1992 cases are not included in Table 2 because only a small proportion which may not be representative was available for independent assessment.
Because of incomplete data for the pre-accident cases no direct comparisons can be made. However, it is known that only 1 out of the 9 cases (11%) diagnosed in the ten-year period preceding the accident was below 10 years of age at diagnosis, a significantly ($p = 0.011$ by Fisher exact test) lower proportion than among the cases diagnosed from 1986 to 1991 (60%). Forty-four (51%) of the 86 cases with confirmed histology were a few months to 4 years old at the time of the accident. Among the cases diagnosed from 1988 onwards none was born after 1986.
In order to investigate whether there was an effect of screening activities on tumour and patient

Location/ year	No of cases Reported	Histology reviewed (% of reported)		Histology confirmed (% of reviewed)		Incidence (95% Confidence Intervals) per 100,000 person-years based on reported cases	
Belarus *pre-Chernobyl*							
1976–1985	9	na		na		0.041	(0.019–0.078)
Belarus *post-Chernobyl*							
1986	2	1	(50%)	1	(100%)	0.083	(0.010–0.300)
1987	3	3	(100%)	0	(0%)	0.124	(0.026–0.362)
1988	7	5	(71%)	3	(60%)	0.290	(0.117–0.598)
1989	6	6	(100%)	6	(100%)	0.249	(0.091–0.542)
1990	27	23	(85%)	23	(100%)	1.148	(0.757–1.670)
1991	55	55	(100%)	53	(96%)	2.335	(1.759–3.039)
1992	60	27	(45%)	27	(100%)	2.548	(1.944–3.280)
1986–1992	160	120	(75%)	113	(97%)		
International comparison							
Eastern Europe[1]	21	na		na		0.072	(0.045–0.110)
Scandinavia[2]	41	na		na		0.194	(0.139–0.263)
U.S.A. SEER (Whites)[3]	37	na		na		0.194	(0.137–0.268)
na: not available							

[1] Bohemia and Moravia 1983–1887; Slovakia 1983–1987; Estonia 1983–1987; Latvia 1983–1987; Cracow 1983–1986; Lower Slesia 1983–1986; Nowy Sacz 1983–1986; Opole 1985–1987; Warsaw 1983–1987[14]

[2] Denmark 1983–1987; Finland 1982–1986; Norway 1983–1987; Sweden 1983–1987[14]

[3] U.S.A., SEER (Surveillance, Epidemiology and End Results Program): Alameda County, San Francisco Bay Area, Connecticut, Atlanta, Hawaii, Iowa, Detroit, New Mexico, Utah, Seattle (Whites) 1883–1987[14].

Table 1. *Incidence of thyroid cancer in children below 15 years of age in Belarus 1976–1985 (pre-Chernobyl), 1986–1992 (post-Chernobyl) and international comparison rates*

characteristics, the cases diagnosed in the period before screening began (1986 to 1989) were compared with the cases reported in 1990 and 1991 (Table 3). No statistically significant differences are evident although there is a trend towards younger age, more diagnoses in Gomel *oblast*, and smaller tumours during the later years when screening of children at schools and clinics took place. The severity of disease at diagnosis as judged from lymph node involvement and distant metastasis was similar in the two periods.

Figure 1a shows incidence rates for childhood thyroid cancer for 1990 and 1991 combined by *oblast* or groups of districts. The highest rate is observed in the districts adjacent to Chernobyl but high rates are seen in all of Gomel and in the neighbouring districts of Mogilev and Brest to the north and west respectively. The geographical distribution of childhood thyroid cancer incidence thus roughly corresponds with the contamination pattern shown in Figure 1b, although no

Characteristic	year 1986 (n = 1)	1987 (n = 0)	1988 (n = 3)	1989 (n = 6)	1990 (n = 23)	1991 (n = 53)	total (n = 86)	
Age (years)								
0–4	0	–	0	1	2	0	3	(3.5%)
5–9	0	–	2	1	15	31	49	(56.9%)
10–14	1	–	1	4	6	22	34	(39.6%)
Sex								
F	1	–	2	2	10	34	49	(57.0%)
M	0	–	1	4	13	19	37	(43.0%)
Residence at diagnosis								
Gomel	1	–	1	2	11	37	52	(60.5%)
Brest	0	–	1	1	5	4	11	(12.8%)
Minsk	0	–	0	1	3	5	9	(10.5%)
Mogilev	0	–	0	0	3	2	5	(5.8%)
Grodno	0	–	1	2	0	3	6	(7.0%)
Vitebsk	0	–	0	0	1	2	3	(3.5%)
TNM classification								
T (tumour)								
<1 cm (T1)	0	–	0	0	2	9	11	(12.8%)
1–4 cm (T2)	0	–	2	2	7	8	19	(22.1%)
>4 cm (T3)	0	–	1	0	1	1	3	(3.5%)
beyond capsule (T4)	1	–	0	4	13	35	53	(61.6%)
N (lymph node metastasis)								
none (N0)	0	–	2	2	7	19	28	(32.6%)
ipsilateral (N1a)	1	–	0	3	7	20	31	(36.0%)
other (N1b)	0	–	1	1	9	14	25	(29.1%)
M (distant metastasis)								
none (M0)	1	–	3	5	19	47	75	(87.2%)
yes (M1)*	0	–	0	1	4	6	11	(12.8%)

* all lung metastasis, including follow-up information

Table 2. *Characteristics of 86 histologically confirmed thyroid cancer cases below 15 years of age in Belarus, 1986–1991*

increase in incidence is noticeable in Grodno *oblast* despite fairly high contamination levels.

Discussion

The nature of the reported increase of childhood thyroid cancer has been the subject of intense debate. Some believe that the excess is real and most likely attributable to radiation released following the nuclear accident at Chernobyl, while their opponents have dismissed it as an artefact.

We have examined three key questions which are at the heart of this debate. First, could the observed increases be spurious due to false positive histological diagnoses? Based on the data presented here and on data published earlier[13], this possibility can clearly be ruled out. In over 90% of reviewed cases the histological diagnosis was confirmed by an international team consisting of a senior pathologist from the Lesnoj Research Institute and two senior Swiss pathologists. Secondly, could the increase be due to more complete case reporting in the post-accident era? Both the leading American and European cancer registries (the SEER-programme in the United States and the Scandinavian registries) report a childhood thyroid cancer incidence rate of 0.19 cases per 100,000 per year (95% confidence interval: 0.14–0.27 and 0.14–0.26)[14], and this rate is significantly lower than the rates reported for Belarus in 1990, 1991 and 1992 ($p<0.05$, $p<0.0001$ respectively). Improved reporting could thus only explain a small part of the increase observed in Belarus.

Thirdly, could a large proportion of the Belarus cases correspond to dormant and thus irrelevant occult papillary carcinoma (OPC) detected by screening? Autopsy studies have shown that OPC is indeed very common in adults. In 8 series comprising 1.759 autopsies OPC was found in 17.6%[9] and a recent autopsy study from Belarus reported a prevalence of 8.8% among 215 autopsies[15]. Conversely, OPC appears to be rare in children but no large autopsy series exists in this age group. The limited data which are available indicate that OPC is present in less than 5% of children[16]. However, even if only one out of a hundred children were affected, this could lead to a spurious epidemic of thyroid cancer if OPC was detectable by screening and if a large enough number of children were screened. The exact number of children screened is unknown but it is certain that many children were indeed examined for thyroid disease by palpation or ultrasonography. These activities were concentrated in the southern, most heavily contaminated regions of Belarus, from which the majority of cases have been reported.

A number of observations make it nevertheless unlikely that OPC detected by screening is behind the observed increase in childhood thyroid cancer in more than a minority of cases. In the autopsy studies mentioned earlier OPC was detected by serially and transversally cutting the thyroid at 2- to 3-mm intervals. Eighty-one percent of occult tumours measured less than 3 mm in diameter and 96% measured below 10 mm[9]. The same holds true for a study from Belarus: 46% of OPCs were up to 1 mm in size and only one (4%) was larger than 5 mm[15]. It is therefore unlikely that more than a small proportion of occult tumours would be detectable by screening. Furthermore, the histological features found in Belarus are far from typical for OPC. Among the histologically confirmed cases diagnosed in 1990 and 1991, 70% measured more than 10 mm, 62% showed extracapsular growth and 66% lymph node metastasis, and after follow-up, 13% had distant metastasis of the lung. During the

Characteristic	**period** **1986–1989** ***(No or little screening)*** **n = 10**	**1990–1991** ***(Screening)*** **n = 76**	**p***
Age (years)			
0–4	1 (10%)	2 (2%)	0.13
5–9	3 (30%)	46 (61%)	
10–14	6 (60%)	28 (37%)	
Sex			0.9
F	5 (50%)	44 (58%)	
M	5 (50%)	32 (42%)	
Place of residence			0.29
Gomel	4 (40%)	48 (63%)	
Other	6 (60%)	28 (37%)	
TNM classification			
T (tumour)			0.19
< 1 cm (T1)	0 (0%)	11 (14%)	
1–4 cm (T2)	4 (40%)	15 (20%)	
>4 cm (T3)	1 (10%)	2 (3%)	
beyond capsule (T4)	5 (50%)	48 (63%)	
N (lymph node metastasis)			0.8
none (N0)	4 (40%)	26 (34%)	
ipsilateral (N1a)	4 (40%)	27 (36%)	
other (N1b)	2 (20%)	23 (30%)	
M (distant metastasis)			1.0
none (M0)	9 (90%)	66 (85%)	
yes (M1)**	1 (10%)	10 (15%)	

* by Student's t-test, Fisher's exact test or continuity adjusted chi-square test

** all metastasis of the lung

Table 3. *Comparison of thyroid cancer cases diagnosed 1986–1989 (no or little screening) with cases diagnosed 1990 and 1991 (some screening)*

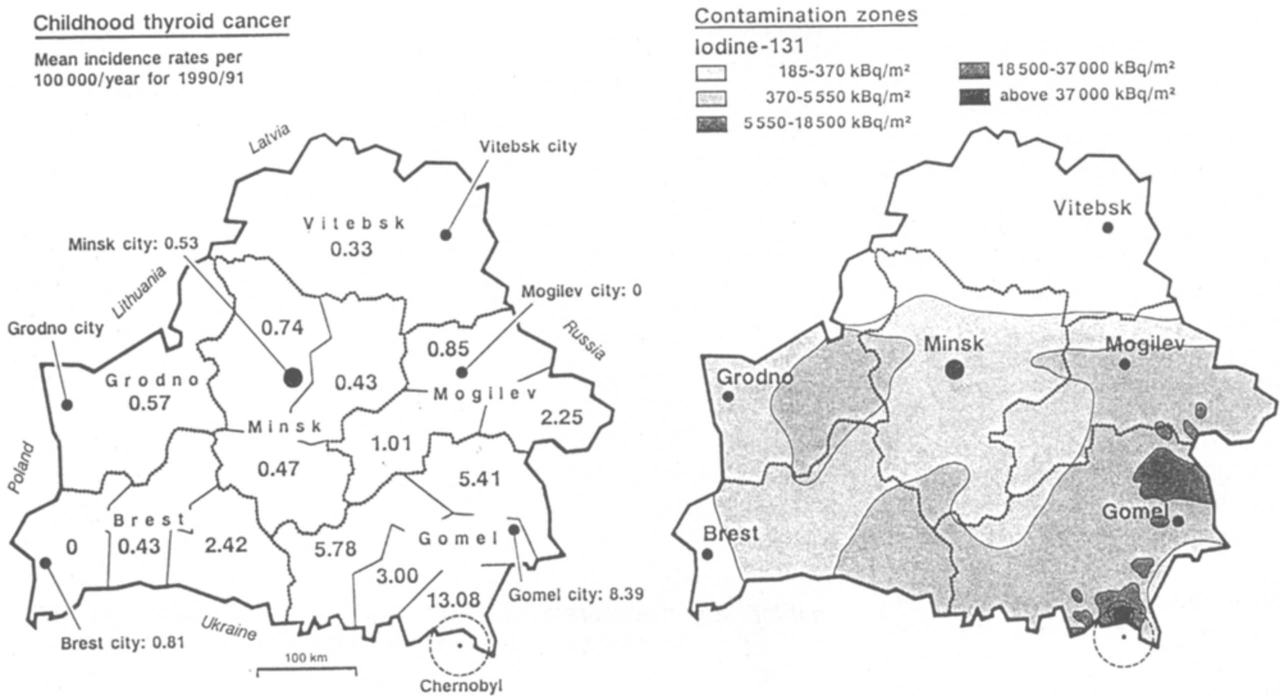

Figure 1. *Incidence of thyroid cancer in children up to 15 years of age per 100,000 person-years for 1990 and 1991 combined (Figure 1a) and iodine-131 contamination map of Belarus (Figure 1b). Belarus is divided into oblasts (..........); the southern oblasts were further divided into groups of districts (-------). The circle around Chernobyl indicates a 30 km radius*

follow-up period one child died from lung metastasis. These findings are very comparable to those for a series of childhood thyroid cancer patients treated in France[17].

The reports to the registry thus appear to reflect a real increase in incidence of childhood thyroid cancer, although this conclusion should be further supported by studies specifically addressing the question of screening. Is this increase compatible with causation by radiation from the nuclear accident? Radioactive iodines accumulate in the thyroid gland and the risk of developing radiation-induced thyroid cancer will thus depend on levels of exposure to radioiodines. Individual radioiodine doses are difficult to reconstruct, given the short half-life of radioactive iodine isotopes, and attempts at developing such estimates are still in progress. However, geographical comparisons are already possible. The regional distribution of iodine-131 contamination as estimated for May 10, 1986, by the Belarus Centre for Radiation Control and Environmental Radiation Surveillance, is shown in the figure. A similar map had already been produced from data of the Lawrence Livermore National Laboratory in 1986[18]. The geographical distribution of childhood thyroid cancer incidence roughly corresponds to this contamination pattern.

The age distribution of the cases also supports a causal link with the accident. In the pre-accident era, only 1 out of 10 children was below the age of 10 years at diagnosis, but this proportion increased to over 50% among the cases reported in 1990 and 1991. Fifty-four percent of the latter were less than 5 years old in 1986, but none of the cases diagnosed between 1988 and 1991 were born after 1986. These data are compatible with causation by radiation and with a higher susceptibility among younger children. No increase in thyroid cancer had been seen in adult patients after iodine-131 treatment, but external radiation to the thyroid is more carcinogenic in infants than in adults and the same may be true for internal radiation from iodine-131[4, 19]. Finally, papillary histology has been shown to be associated with radiation exposure[3].

In conclusion, our analysis of available data supports the notion that there is a real increase in childhood thyroid cancer in Belarus which is causally related to the Chernobyl nuclear accident, as tumour properties make it unlikely that more than a minority of cases correspond to occult carcinoma detected by screening. This interpretation corresponds to that of a recent consensus opinion of an international Panel of Thyroid Experts formed by the Commission of the European Community[20], to which some of our analyses had already been made available. It is also compatible with preliminary findings from the Chernobyl Sasakawa Project, where systematic ultrasonic screening of children led to the discovery of seven cancer cases in the contaminated Gomel *oblast* (6.129 children screened), but so far none in Mogilev *oblast*, which was much less contaminated by iodine-131 (6.496 children screened)[21].

Nevertheless, as is evident from numerous discussions, the evidence will not be generally considered as conclusive, and further analyses including data on the extent of screening activities, the mode of diagnosis of reported cases, and the place of residence of the patients around the time of the Chernobyl accident are needed, as are studies attempting to establish exposure levels, dose-response relationships for Chernobyl-related thyroid cancer and possible modifying factors including endemic iodine deficiency.

In the meantime, the ongoing debate should not distract those who are in a position to help from providing urgently needed medical and humanitarian assistance to the increasing number of Belarus children in whom thyroid cancer has been diagnosed.

Zusammenfassung

Schilddrüsenkrebs in Belarus nach Tschernobyl: Verbesserte Erkennung oder erhöhte Inzidenz?

Es wird diskutiert, ob die berichtete Zunahme von Fällen kindlichen Schilddrüsenkarzinoms in Belarus echt und der Strahlung in der Folge des Nuklearunfalls von Tschernobyl zuzuschreiben ist, oder ob es sich um einen Artefakt handelt, indem nach dem Unfall falsche histologische Diagnosen gestellt wurden, die Berichterstattung über die Fälle vollständiger wurde oder Massenfrüherfassungsaktivitäten bei Kindern durchgeführt wurden. Wir haben die histologischen Präparate von 120 (75%) der 160 Fälle von Schilddrüsenkarzinom bei Kindern bis zu 15 Jahren überprüft, die zwischen 1986 und 1992 dem Krebsregister von Belarus gemeldet worden sind, sowie die zeitliche Entwicklung und geographische Verteilung der aufgetretenen Fälle und deren Merkmale analysiert. Gestützt auf die gemeldeten Fälle nahm die Inzidenzrate von 0,041 pro 100000 im Jahre 1986 auf 2,548 im Jahre 1992 zu. In 94% der überprüften Fälle wurde Krebs als Diagnose bestätigt. Mit einer Ausnahme von medullärem Karzinom wurden nur papilläre Karzinome gefunden. Die Mehrzahl der Tumoren hatte die Organkapsel durchbrochen und massen über 10 mm im Durchmesser. Im Laufe der Zeit fand sich ein schwacher und statistisch nicht signifikanter Trend (p = 0,19) in Richtung kleinerer Tumoren. Der Anteil von Tumoren mit Lymphknoten- und entfernten Metastasen blieb unverändert. Gestützt auf die histologisch bestätigten Fälle war die Inzidenz angrenzend an Tschernobyl und in westlicher und nördlicher Richtung am höchsten, was auch der Kontamination mit Jod-131 entspricht. Unsere Daten weisen damit deutlich darauf hin, dass die beobachtete Zunahme echt ist, doch werden noch weitere Daten benötigt, um das Ausmass des Einflusses des Massenscreening abzuschätzen und die mögliche Beziehung mit der im Jahre 1986 in Tschernobyl freigesetzten radioaktiven Strahlung abzuklären.

Résumé

Le cancer de la thyroïde en Belarus après Tchernobyl: Détection améliorée ou incidence accrue?

La question est posée de savoir si l'augmentation du nombre de cas de cancer de la thyroïde observée chez les enfants en Belarus est réelle et à attribuer à l'irradiation relâchée suivant l'accident nucléaire de Tchernobyl, ou si elle reflète un phénomène artificiel dû à un diagnostique histologique erroné, une déclaration de cas plus complète ou le résultat des campagnes de dépistage qui ont suivi l'accident. Nous avons examiné les préparations histologiques de 120 (75%) des 160 cas survenus chez les enfants de moins de 15 ans rapportés entre 1986 et 1992 au registre des tumeurs de la république de Belarus, et analysé les chronologiques et les distributions géographiques de l'incidence et des caractéristiques des tumeurs. L'incidence des cas déclarés a augmenté de 0,041 par 100000 en 1986 à 2,548 en 1992. Le diagnostique de carcinome a été confirmé dans 94% des tumeurs re-examinées. A l'exeption d'un seul cas de carcinome médullaire, toutes les histologies étaient du type papillaire. La plupart des tumeurs s'étandaient au delà de la capsule de l'organe, et avaient un diamètre supérieur à 10 mm. Pour les années les plus récentes, les tumeurs mesurées au moment du diagnostique sont devenues légèrement et non-significativement (p = 0,19) plus petites. La proportion des tumeurs ayant développé des métastases lymphatiques ou pulmonaires n'a pas changé. L'augmentation de l'incidence des cas confirmés a été particulièrement importante dans le voisinage, ainsi que dans l'ouest et le nord de Tchernobyl, ce qui correspond assez bien à la distribution de la contamination par l'iode-131. Nos données suggèrent donc fortement que l'augmentation observée et réelle. Néanmoins, d'avantage de données sur le dépistage en masse sont nécessaires pour clarifier l'association possible avec l'irradiation consécutive à Tchernobyl en 1986.

Acknowledgements

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Reference 6

Peer reviewed article

Chronic Cs-137 incorporation in children's organs

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Summary

In Belarus's Gomel region, which was heavily contaminated by fallout from the Chernobyl disaster, we have studied the evolution of the Cs-137 load in the organisms of the rural population, in particular children, since 1990. Children have a higher average burden of Cs-137 compared with that of adults living in the same community.

We measured the Cs-137 levels in organs examined at autopsy. The highest accumulation of Cs-137 was found in the endocrine glands, in particular the thyroid, the adrenals and the pancreas. High levels were also found in the heart, the thymus and the spleen.

Key words: Chernobyl children; radiocaesium; thyroid; adrenals; pancreas; thymus; myocardium

Introduction

Children who have lived in radiocontaminated districts of Belarus since the explosion of the Chernobyl atomic power plant (26 April 1986) suffer from chronic diseases rarely encountered in children from areas of Belarus not contaminated with Cs-137. Much has been written on the pathogenic role of the so-called radioiodine shock, which is due to some tens of short-lived radionuclides the principal of which is iodine-131. The iodine shock may also initiate processes which continue to evolve under chronic low-level radiation due to incorporated Cs-137. The artificial radioactivity which has persisted for the last 17 years in the organisms of people living round Chernobyl is due to long-lived radionuclides, mainly strontium (Sr-90), caesium (Cs-134 and especially Cs-137) and uranium derivatives including plutonium.

When studying the effect of Cs-137 in children it is important to select those born after March 1987 who have not suffered from the iodine shock even *in utero*. During normal pregnancies, the placenta takes up circulating Cs-137 in the maternal blood protecting the foetus. If the Cs-137 concentration in the placenta exceeds 100 Bq/kg, the foetus suffers.

Newborns take up Cs-137 in the maternal milk. Children drinking cow's milk and vegetables produced in local villages accumulate increasing amounts of Cs-137. The highest Cs-137 concentration is found in wild berries, mushrooms and game, which are an important resource for poor families.

Methods

Methods used at Gomel Institute of Pathology

Caesium is both a gamma and a beta emitter. Since beta rays are more radiotoxic for the genome and cell structures than gamma rays, the latter are used to measure the specific activity of caesium in humans. For either whole body measurement or during autopsies we used different equipment to measure the level of Cs-137 accumulated in various organs.

The accuracy of measurements by the mobile teams of the Belrad Institute, the independent radioprotection agency, is guaranteed by compulsory annual state inspection of the equipment. Furthermore, as part of a joint German-Belarussian project it was possible by intercalibrations to verify the different items of equipment (the 7 whole-BC "Screener-3M" of Ukrainian origin from the Belrad Institute, and the 2 mobile whole-BC laboratories of Juelich Research Centre ["Canberra Fastscan Whole BC", Germany]). While initially the error limit was as high as 11%, later it did not exceed 7%. Below 5 Bq/kg bodyweight measurements become less accurate.

For laboratory measurement of specific activity in samples, such as organs examined during autopsy, Belrad provided Gomel State Medical Institute with automated Rug-92M gamma radiometers. The duration of measurement is one minute for samples >100 Bq/kg and 10 minutes for samples of 50–100 Bq/kg. Below 49 Bq/kg precision decreases. Samples were also doubled-checked in France to validate the findings.

No financial support declared.

Results and discussion

Anatomo-pathological approach

At the Institute of Pathology the Cs-137 concentration was systematically measured in different organs. Throughout pregnancy the foetus appears to be relatively well protected by the placenta, which takes up and accumulates circulating Cs-137 from the blood of the mother. High foetal levels of Cs-137 were found in cases of abortion with multiple malformations.

High levels were found in infants aged up to six months. Table 1 shows Cs-137 levels in 13 organs of infants.

Cs-137 accumulation in organs of adults and children

We studied at autopsy the level of Cs-137 incorporated in eight different organs of adults and children residing in rural areas of the Gomel region. The average levels of Cs-137 measured were two to three times higher in the organs of children than in those of adults living in the same environment (Figure 1).

In all organs examined the average levels of radiocaesium were higher in children than in adults. In rural communities of the Gomel oblast the average whole body count was also higher in schoolchildren than in adults.

Figure 1

Radioisotopes accumulation in the organs of adults and children, died in 1997:
1: myocardium;
2: brain;
3: liver;
4: thyroid gland;
5: kidneys;
6: spleen;
7: skeleton muscles;
8: small intestine.

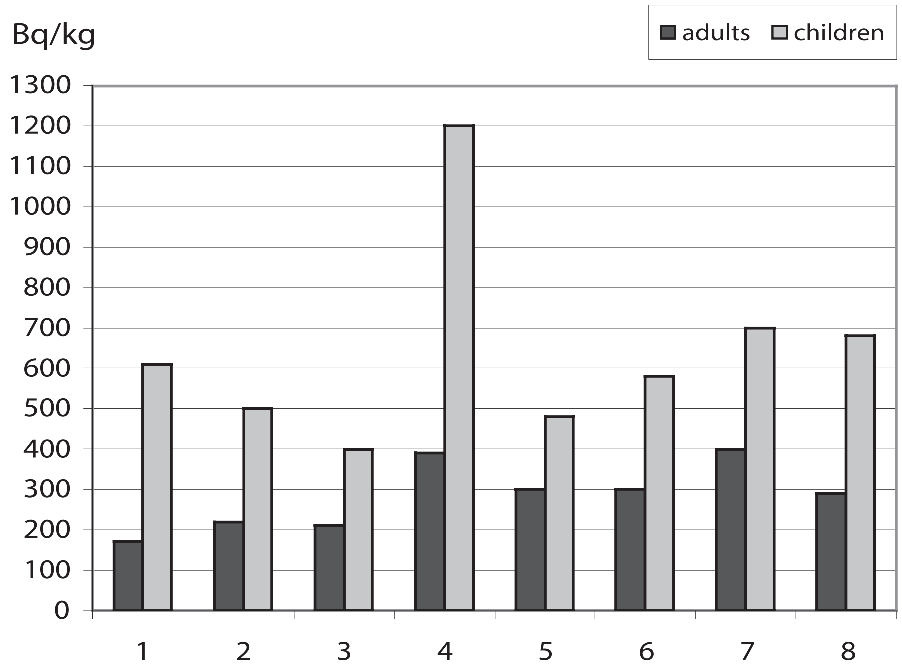

Table 1

Cs-137 level measured in 13 organs of 6 infants. Very high specific activity of Cs-137 is found in pancreas, adrenals, heart, but also thymus, stomach and intestinal wall. In cases 1 and 2 the concentration of Cs-137 in the pancreas is respectively 44 and 45 times that in the liver.

	1	2	3	4	5	6
Cause of death:	sepsis	premature malform.	sepsis bleeding	cerebral malform.	cardiac	sepsis
Organs:						
heart	**5333**	4250	625	**4166**	1071	1491
liver	250	277	525	851	882	1000
lung	1125	2666	400	1195	1500	2610
kidneys	1500	1687	259	2250	812	583
brain	3000	1363	305	90	1693	714
thyroid gland	4333	**6250**	250	1900	n.d.	1583
thymus	3000	3833	1142	**3833**	714	833
small intestine	2500	1375	571	3529	2200	590
large intestine	3250	3125	261	3040	**4000**	2125
stomach	3750	1250	**1500**	n.d.	n.d.	n.d.
spleen	3500	1500	428	1036	2000	2125
adrenals	1750	2500	n.d.	2500	**4750**	**2619**
pancreas	**11 000**	**12 500**	**1312**	n.d.	n.d.	**2941**

n.d. = not done
The highest two values are underlined in each case

Table 2

Average levels of specific activity of Cs-137 in 13 organs of 52 children aged up to 10 years from the Gomel region in 1997.The highest average Cs-137 levels are found in the endocrine glands including the pancreas. The Cs-137 concentration in the thyroid gland is 6 times that in the liver. Next to the endocrine glands comes the thymus, with an average of 930 Bq/kg.

Organ	Bq of Cs-137/kg
1. Thyroid	2054 ± 288
2. Adrenals	1576 ± 290
3. Pancreas	1359 ± 350
4. Thymus	930 ± 278
5. Skeletal muscle	902 ± 234
6. Small intestine	880 ± 140
7. Large intestine	758 ± 182
8. Kidney	645 ± 135
9. Spleen	608 ± 109
10. Heart	478 ± 106
11. Lungs	429 ± 83
12. Brain	385 ± 72
13. Liver	347 ± 61

Children aged up to 10 years studied in 1997

From April 26 to June 1986 the radioactive fallout from Chernobyl was intense. Two-thirds of the radioactivity was due to short-lived radionuclides, the most important of which was iodine-131. Children born after March 1987 did not suffer from this "iodine shock" even *in utero*.

At the Institute of Pathology we studied 51 children from Gomel rural communities who had died from various causes. This group had not had iodine shock. If chronic internal irradiation was responsible for these children's pathology it would be ascribable to long-lived radionuclides such as radiocaesium. The decreasing average levels, with the standard deviation for the 13 organs tested, are shown in Table 2.

The Medical State Institute of Gomel studied cellular damage caused by the accumulation of radiocaesium in organs. The functional disorders or diseases caused by chronic accumulation of this radionuclide in organs were presented in 20 theses based on clinical, epidemiological, anatomopathological or experimental studies in rats and hamsters [1–4].

Conclusion

The Cs-137 burden in the organisms of children must be further investigated and the pathogenesis of different diseases intensively studied. This is an urgent need, as radiocontaminated agricultural land is being increasingly cultivated and radiocontaminated food is circulating countrywide.

Schoolchildren in contaminated areas received radiologically clean food free of charge in school canteens and spent a month in a sanatorium, in a clean environment, each year. For reasons of economy the annual sanatorium stay has been shortened, and communities in some contaminated areas have been classified as "clean", thus ending the supply of clean food from the state.

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Reference 7

Investigation of Strontium-90 intake in teeth of children living near Chernobyl

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Introduction

The catastrophe in reactor block no 4 of the nuclear power plant of Chernobyl resulted in a release of radioactive material. This fallout affected especially the region of Chernobyl, but also whole Europe and could be detected worldwide. Certain radioactive nuclides such as jodine (^{131}I, ^{129}I), cesium (^{137}Cs, ^{134}Cs) and strontium (^{90}Sr, ^{89}Sr) as well as plutonium and americium nuclides mainly contributed to the contamination of man and environment.

Even 20 years later experts dispute about the consequences of this radioactive exposition of man (IAEA report, IPPNW report). The effects of the radioactive iodine nuclides on an increased incidence of thyroidal cancers in exposed populations could be proven (Prof. Edmund Lengfelder of the Otto Hahn Strahleninstitut Munich). Longterm effects caused by ^{137}Cs and ^{90}Sr cannot be definitely estimated. Incorporated ^{137}Cs will spread throughout in the whole body. Whereas ^{90}Sr will be deposited mainly in teeth and bones, that close to the marrow, where blood formation can be disturbed (leukaemia).

Considerable activities can be detected in the affected areas even 20 years after the catastrophe and are ubiquitary spread in every compartement of the biosphere. Food is contaminated more or less according to type and origin. The gamma nuclide ^{137}Cs can be analysed easily and therefore is investigated intensively. Biological half-life and behaviour of cesium are well documented for every compartement and man (whole body countings). ^{90}Sr is a pure β-emitter and can be analysed only after chemical extraction procedures. As a consequence ^{90}Sr is analysed only rarely.

This lack of data leads to the general uncertainty of the exposed population and even of scientists. Strontium is much more mobile than cesium and shows a quite different fate in the biosphere. Analyses of primary teeth can illustrate the incorporated activity of ^{90}Sr in a more differentiated way. Particulary during the organogenesis of the foetus after 6 months up to 6 months after birth the child incorporates ^{90}Sr. Once incorporated the strontium remains in the body and is excreted only slowly. The biological half-life of ^{90}Sr is 11 years.

The intake of ^{90}Sr of the exposed population could be estimated with the help of suppositions on the basis of analytical data from food and environmental samples. In this report first results of a project of many years duration of ^{90}Sr analyses of primary teeth of children from the most affected regions around Chernobyl are presented. These original results are compared with analyses of teeth from Swiss children. A further outlook will be presented at the end.

Materials and methods

Samples

During the last 15 years many children from the surrounding area of Chernobyl received free sanitation of their teeth in Switzerland. Primary teeth from 64 children were collected during these dental treatments. The teeth were preserved with formaldehyde and sent to the lab. The children were born between 1977 and 1991 in villages in the region of Chernobyl (i.e. Luginy, at a distance of 80 km from Chernobyl). Their primary teeth were collected during the years 1991 to 1998.

Fig. 1 *Primary tooth samples from children of Luginy*

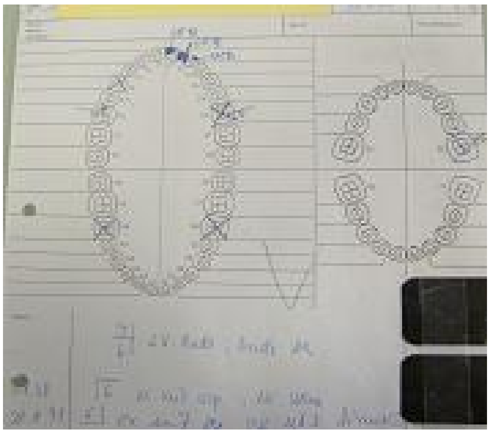


Fig. 2 *A protocol from a dental treatment*

Radioactivity of ^{90}Sr

The activity in radioactivity is defined as:

Activity $A = \dfrac{\ln 2 * m}{T_{1/2} * A_r}$

Whereas the specific activity is defined as the quotient of activity and mass:

$$A_{spec} = \frac{\ln 2}{T_{1/2} * A_r}$$

Ar: relative atomic mass (g), $T_{1/2}$: half live (s),
m: mass weight of the pure carrier-free nuclide

Nuclides with short half lives show high specific acitivities but their masses are infinitely small. ^{90}Sr with a half live of 28.5 years has a mass of 1.94 µg per 10 MBq rsp. 1,94 pg/Bq. ^{90}Sr in the low Bq level corresponds to analytical concentrations in the pg/L range and therefore are difficult to detect with ICP-MS. Due to such very low concentration levels it is necessary to work with carrier nuclides (inactive isotope of the same element) to avoid substantial losses of nuclides by adsorption onto glass walls.

^{90}Sr decays to ^{90}Y which has a short half-life of 65 hours to produce the stable ^{90}Zr. Already after 19 days (seven half-life periods of the radiocuclide ^{90}Y) the secular equilibrium between ^{90}Y and its daughter nuclide ^{90}Y is reached.

Principle of the method

In biological systems the element strontium behaves quite similarly to calcium. The concentration of Ca in most of the biological tissues (especially bones and teeth) is remarkably constant. The ratio of Sr / Ca in the tissues is admittedly representative for this ratio in the diet. So the activity of ^{90}Sr is usually reported in relation to the ca-content (Bq ^{90}Sr / g Ca). Teeth are the only calcified biological tissue which can be ethically obtained because the primary teeth are expelled spontaneously or have to be extracted for health reasons.

The collected teeth are mineralised and both nuclides ^{90}Sr and ^{90}Y are extracted from the ashes by precipitation as oxalate salts. The nuclide ^{90}Y is then separated from ^{90}Sr by adding inactive ^{88}Y as a carrier and precipitation of the total yttrium as yttrium hydroxide. After redissolving and precipitation as yttrium oxalate the β-decay of the ^{90}Y is immediately measured with a gas proportional counting system. The ^{90}Sr activity of the precipitate is recalculated to the time of the last precipitation via decay curve of the ^{90}Y source. The original ^{90}Sr of the sample is recalculated considering the overall chemical recovery of the several precipitation steps,

counting efficiency of the gas proportional counter and calculated the activity back to the birth date.
Ca was determined with inductively coupled plasma mass spectrometry (ICP-MS).

Sample preparation
The teeth were washed carefully with distilled water and air dried at ambient temperature over night.

Mineralisation of the tooth samples
At least 0.5 g of tooth was necessary for the determination of the ^{90}Sr activity. In some cases teeth from children of the same year of birth had to be pooled to get enough material for the analyses. The material was weighed into a porcelain crucible and ashed for 20 hours at 600 °C. Remaining particles were pounded and ashed again for 3 hours at 600 °C. The final greyish-white ashes were dissolved in 20 ml hydrochloric acid (33% w/w) and the solution was filtered into a volumetric flask using a paper filter and then diluted with distilled water up to 50 ml. 10 ml of the sample solutions were used for the ICP-MS analyses.

First oxalate precipitation
5 ml of a ^{89}Y carrier solution (9 g/l yttrium chloride) were added to 40 mL of this solution and heated to boiling. 6 g of oxalic acid were added carefully to the solution. The oxalates of calcium, strontium and yttrium were precipitated by adding 150 ml of a solution of ammonium acetate (100 g/l) until a pH of 5 was reached. After adding further 15 ml of ammonium acetate the solution was cooled to room temperature.

Yttrium hydroxide precipitation
The precipitate was filtrated by means of a glass sinter filter and washed with ammonium oxalate solution (1g/l w/w). The filter and the precipitate were dried using an infrared lamp and then mineralised for 4 h at 600 °C in a muffle furnace. The ashes was dissolved in 10 ml hydrochloric acid solution (20 % w/w) and diluted with water to 100 ml. 5 ml of a ^{88}Sr carrier solution (50 g/l strontium chloride) and 4 drops of methyl orange indicator solution were added to the solution and then heated to boiling. Ammonium hydroxide solution (25 % w/w) was added until the colour changed to yellow (pH>5). A further ml of ammonium hydroxide solution was added and the solution boiled for 10 minutes. The precipitation was then filtrated through a glass sinter filter and washed with diluted ammonium hydroxide solution. Date and time of the precipitation was noted. At this moment the ^{90}Y activity corresponds to the ^{90}Sr activity in equilibrium and the decay of the isolated ^{90}Y starts.

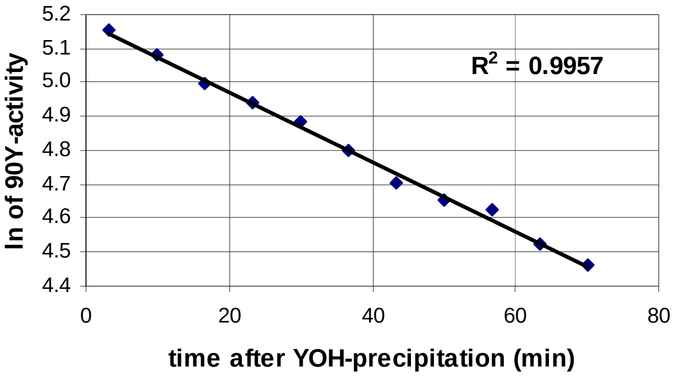
Yttrium oxalate precipitation
Then followed a second precipitation of the yttrium with oxalic acid to obtain a pure yttrium source. The precipitate was resolved by washing the filter with three portions of 3 ml of hydrochloric acid (20 % w/w) into a 200 ml Erlenmeyer flask. The filter was washed with distilled water and 5 drops of methyl orange indicator solution were added. Ammonium hydroxide solution (10 % w/w) was added to the solution until the colour changed to yellow (pH>5). By adding hydrochloric acid (20 % w/w) dropwise the pH of the solution was lowered to a pH of 1 to 2 (colour changed to red). The solution was heated to boiling and 8 ml of oxalic acid (20 g/l) were added. The precipitate was heated for a further 10 minutes and then cooled to room temperature. The precipitation was filtered off by use of a Millipore filter and washed with water, ethanol and diethyl ether. The yttrium oxalate was dried for 15 minutes at 105 °C and weighed. The weighing allowed the calculation of the overall chemical recovery of all precipitation steps. The YOH precipitation was finally fixed with collodium solution onto a metal disc for the β-analyses.

β-spectrometry
The β-analyses were started immediately after the preparation of the yttrium source. 4 samples were measured in parallel for at least 7 consecutive cycles of 400 minutes each. The original ^{90}Sr activity was recalculated by extrapolating graphically the β-activity to the final time of the

last precipitation and by taking into account detector efficiency and overall chemical recovery. Recoveries of the precipitation procedures were from 70 to 90 %. Teeth from children of Basel were spiked with ^{90}Sr and analysed. Total recovery was 103 % after correction of the chemical recovery. The results were expressed as quotient of ^{90}Sr in Bq/g Ca.

The β-counter used was a very low background multiple detector for low alpha/beta activities type MINI 20/41 from eurysis measures, Saint Quentin, Yvelines, France. 4 gas flow proportional counters permitted 4 simultaneous alpha and beta measurements. α/β amplitude discrimination of the pulses was applied to distinguish between α- and β-decays. The efficiency of the β-counter was 25%. The background counts were 0.22 counts per minute (cpm). With a counting time of 400 min the minimal detection limit was 0.04 cpm. The detection limit of the method was then about 0.08 cpm rsp. 15 mBq ^{90}Sr/g tooth or 45 mBq ^{90}Sr/g Ca. Total measurement uncertainty was about 30 % whereas the counting uncertainty was about 12 % at an activity level of 30 mBq/g Ca.

Fig. 3
Measured β-activity of a tooth sample. The reconstructed half-life of ^{90}Y (slope of the curve) was 67.2 hours and slightly higher than the theoretical value of 64.5 hours.



ICPMS analyses

10 mL of the hydrochloric acid solution of the mineralised tooth samples were analysed with ICP-MS at the Cantonal Laboratory Basel-Country. The analyses consisted in the determination of the non radioactive nuclides ^{40}Ca, ^{84}Sr, ^{86}Sr, ^{87}Sr and ^{88}Sr. The ICP-MS system was from Perkin Elmer model Elan 6100. Total uncertainty for each nuclide was about 20 %.

Results

The ^{90}Sr activities were calculated back to the date of birth. These 64 results were expressed as Bq ^{90}Sr/g Ca.

Year of birth	Number of samples	Mean value (Bq ^{90}Sr/g Ca)	Standard deviation
1977	1	0.116	
1978	1	0.085	
1979	1	0.180	
1981	1	0.290	
1982	1	0.154	
1983	8	0.213	0.066
1984	10	0.193	0.061
1985	7	0.217	0.146
1986	5	0.229	0.015
1987	6	0.235	0.182
1988	18	0.232	0.009
1989	2	0.109	0.025
1991	2	1.919	0.757
1992	1	0.827	

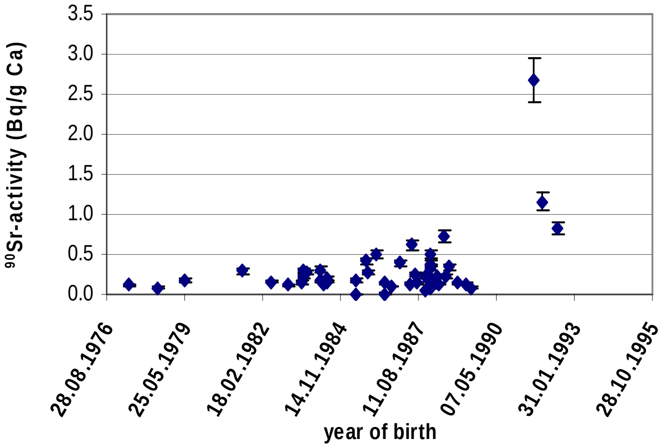


Fig. 4
Development of the ^{90}Sr activity in primary teeth of children from Luginy. The values are given as average of the year of birth and are calculated back to the year of birth.

Comparison with results from Swiss primary teeth

The following figure shows the ^{90}Sr activities in teeth of children from Chernobyl compared with results from Swiss children. The Swiss data are yearly published by the Swiss Federal Office of Public Health[1]. Primary teeth from Swiss children of the cantons of Waadt and Zurich show activities of 0.02 - 0.03 Bq/g Ca. The Swiss date from 1953 to 2002 show clearly a maximum in the 1960 years resulting from the fallout of atomic bomb tests. Activities in teeth of Swiss children reached 0.4 Bq/g Ca whereas the Chernobyl fallout caused a maximum in Switzerland in 1986 of only 0.06 Bq/g Ca.

The investigated Chernobyl teeth show about the ten fold of the Swiss values. An increase of the activity due to the accident at Chernobyl could not be observed.

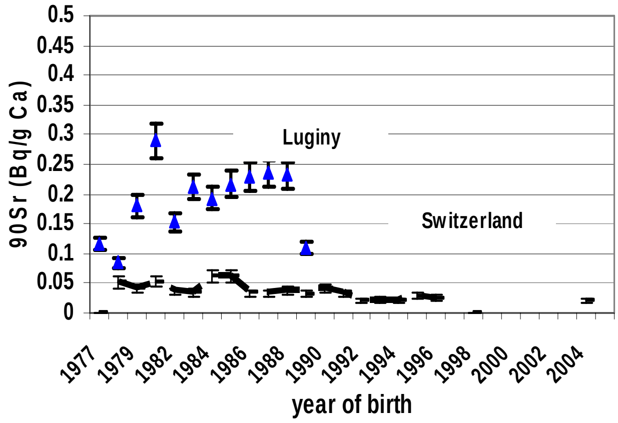


Fig. 5
Comparison of ^{90}Sr activity in primary teeth of children from Luginy and children from Switzerland. All values are mean values and calculated to the year of birth. Two high values in 1991 and 1992 are not shown (see figure 4).

Discussion

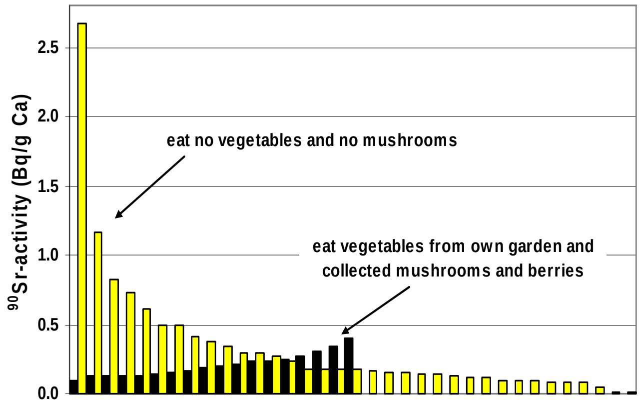
It is quite surprising that the activity of teeth from children in the region of Chernobyl born before 1986 is as high as the activity of the teeth of children born just after the catastrophe. Also if the environment had been continuously contaminated since long time, the input from the accident should produce a measurable augmentation of ^{90}Sr activity. At the moment we think that ^{90}Sr from the contaminated food is more effectively adsorbed by young people, even they are older than 6 years, than admitted so far.

During the sessions with the dentists, parents and children were asked about their eating habits. Half of the children were eating berries from the own garden and / or mushrooms collected in the woods. As the following figure shows there could not be found any correlation between ^{90}Sr activity in the teeth and the eating habits. Children not eating own-grown vegetables, berries or collected mushrooms showed even higher activities.

1 Froidevaux P. et. al.: Mesures de ^{90}Sr dans les vertèbres et les dents de lait in: Environmental radioactivity and radiation exposure in Switzerland. Swiss Federal Office of Public Health, (2005 and further).

Similar high ^{90}Sr activities were found in baby teeth of children living in St. Louis and New York Metropolitan Area from 1957 - 1970[2]. The authors suggest the emissions from local nuclear power reactors as the main source. The observed large variations of the activities can be explained by differences in dietary intake of pregnant women. Temporal variations in reactor emissions from month to month will affect foetal concentrations of radioactivity.
Without a better understanding of the measured values it is not possible to calculate a risk assessment of the ^{90}Sr activity.

Fig. 6
Distribution of ^{90}Sr activities in primary teeth as a function of the eating habits of children from Luginy.



Perspectives

More investigations and discussions are needed to explain the present data. It seems very important to proceed with further measurements of ^{90}Sr activity in teeth of the population in the region of Chernobyl to follow the situation and to understand better the origin of the observed relatively high activity level existing there. The population has the right to know how much radioactive strontium they incorporate and has to be informed also about these aspects of the tragedy.

Acknowledgements

Our thank goes first to the physicians Dres. med. Martin Walter, M. Büttner and M. Gächter for their support with primary teeth from children of Luginy. The authors wish to thank also Hans Schaub from the Cantonal Laboratory Basel-Country for the ICP-MS analyses of the tooth samples, Jean-Jacques Geering for the early ^{90}Sr measurements and Dr. Pascal Froidevaux for support with sr-data, both from the Institute of Applied Radiophysics in Lausanne.

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POSSIBILITIES OF USING HUMAN TEETH FOR RETROSPECTIVE DOSIMETRY: ANALYSIS OF THE TECHA RIVER DATA

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Different methods for utilising teeth were applied for the reconstruction of internal and external doses for the population of the Techa riverside area contaminated as a result of radioactive releases from the Mayak plutonium-production facility. Information on ^{90}Sr content in the enamel of teeth obtained from the Techa River residents has been used for the reconstruction of intakes of this nuclide. Analyses of dosimetric investigations on dental tissues performed in the Techa River region provide an understanding of the possibilities and limitations of using human teeth in retrospective dosimetry studies.

INTRODUCTION

In the dosimetric investigations on the Techa River, where ^{90}Sr was the principal dose-forming radionuclide, the mineralised tissues (depot of ingested Sr) are of the primary interest. The teeth and bones are examples of such tissues, and the dosimetric investigations are mainly based on extensive *in vivo* measurements of ^{90}Sr in body (the skeleton) and in enamel of frontal teeth. Basic features in Sr metabolism obtained with Techa River data(1) provided an opportunity for Sr biokinetic modelling in human bones; reconstruction of ^{90}Sr dietary intake for Techa riverside residents and, as a result, assessment of absorbed doses from ^{90}Sr with the use of the Techa River Dosimetry System (TRDS-2000)(2).

Several studies(3–5) focused on the human teeth as natural dosimeters applicable to the Techa River investigations. As it was shown, the most intensive accumulation of ^{90}Sr in skeletal and tooth tissues occurred at different ages: 12–18 years for the skeleton and 0–5 years for teeth of different positions. The investigations with the use of electron paramagnetic resonance (EPR) technique indicate that extremely high enamel doses (>10 Gy) attributed by ^{90}Sr incorporated in enamel were observed for the age group 0–5 at the onset of ^{90}Sr intakes(3,5). The studies(5) have also demonstrated the principal possibility to use the data on age-dependent ^{90}Sr accretion in child's teeth for reconstruction of the schedule of ^{90}Sr intake in the period of radioactive releases into the Techa River (1950–1956). It should be expected, that the correlation between ^{90}Sr concentrations in tooth enamels and skeleton for children should be significant. The correlation analysis requires careful data selections, since the age-specific changes in ^{90}Sr concentrations in teeth and skeleton are oppositely directed(4)—the appropriate analysis has not been performed in sufficient detail till recent times.

Over the last years of our work on the next version of TRDS the dosimetric databases in URCRM were significantly improved, i.e. all available archival information on residence in contaminated settlements was verified and the results of ^{90}Sr measurements in human body obtained with a whole body counter (WBC)(6) were reassessed. The essential progress in application of EPR technique to dosimetric investigation of human teeth of Techa River residents was also achieved(3) and the total number of teeth measured increased.

Therefore, the main tasks of the present paper are as follows:

(1) To estimate the correlation between ^{90}Sr accumulated in teeth and body (the skeleton) for children based on improved experimental data;
(2) To present the re-evaluated ^{90}Sr dietary intake for Techa River residents based on the improved data on ^{90}Sr measurements in the incisors;
(3) To assess the applicability of ^{90}Sr and EPR measurements in teeth for retrospective dosimetry.

MATERIALS AND METHODS

Gas-flow Geiger–Muller detectors, the so-called Tooth Beta Counters (TBC), were used for *in vivo* measurements of surface-beta activity in front teeth (first and second incisors), in 1959–1997(4,5). These measurements are expressed in relative units and represent the rate of beta counts, i.e. counts per minute (cpm).

The majority of EPR measurements have been performed since 1992 at the Institute of Radiation Protection, GSF-National Research Center for Environment and Health (GSF), under the direction of A. Wieser, and at the Institute of Metal Physics

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(IMP), Ekaterinburg, Russia, under the direction of D. Ivanov. Similar procedures for sample preparation, processing of EPR spectra, and dose estimates with use of universal calibration curve are applied in both Institutes. There were no systematical shifts between their results(7). The contribution made by $^{90}Sr/^{90}Y$ to internal exposure was calculated with the use of Monte-Carlo technique and geometrical model of the teeth(4).

Measurements of ^{90}Sr in the whole body (skeleton) were obtained *in vivo* in 1974–1997 with the use of whole body counter (WBC) that was specially constructed to detect the bremsstrahlung from ^{90}Y(6). Analysis of WBC and TBC data were performed for residents of two settlements located on the Techa River: Metlino and Muslyumovo. The first one evacuated in 1956 was the nearest settlement to the site of releases (7 km). The latter is located in the mid-Techa 78 km downstream and is the nearest non-evacuated settlement to the site of releases.

RESULTS AND DISCUSSION

Comparison of ^{90}Sr accumulations in teeth and skeleton

The data obtained for the Techa River residents allow a detailed analysis of an age-dependent ^{90}Sr accumulation in mineralised tissues (Figure 1a,b). Because extremely high enamel doses measured by EPR technique for children were due to ^{90}Sr in enamel, the EPR data are also presented (Figure 2). Such features were determined earlier; however, the

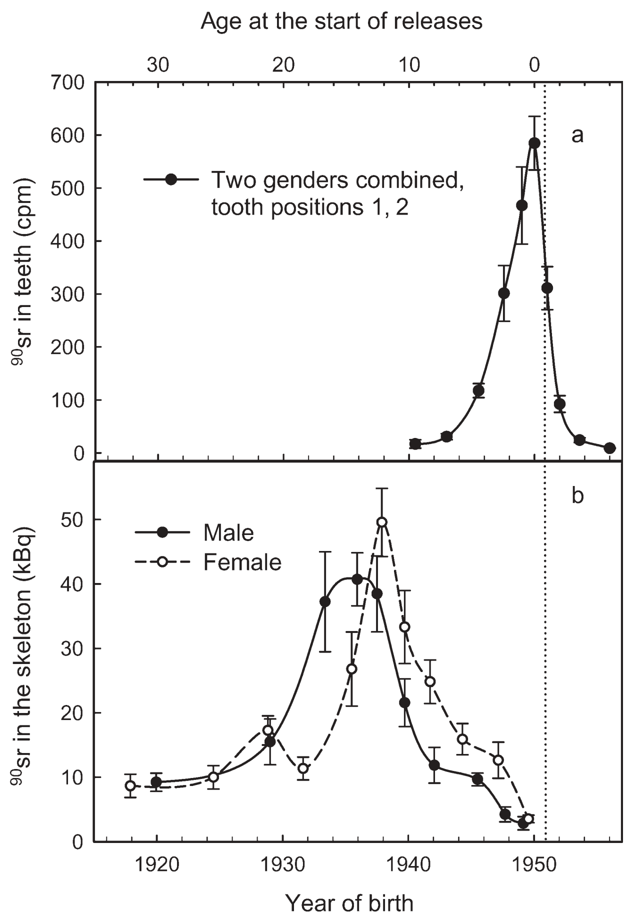

Figure 1. Age-dependent curves of average ^{90}Sr content in incisors (position 1, 2) obtained with TBC in 1977–1980 (a), number of measurements is 272; and of ^{90}Sr contents in the skeleton measured with WBC in 1977–1980 (b), number of measurements is 752 (measurements for Muslyumovo residents). Dotted lines indicate the date of the beginning of releases; bars represent the standard error. For persons born before 1940 the TBC measurements are lower than the detection limit.

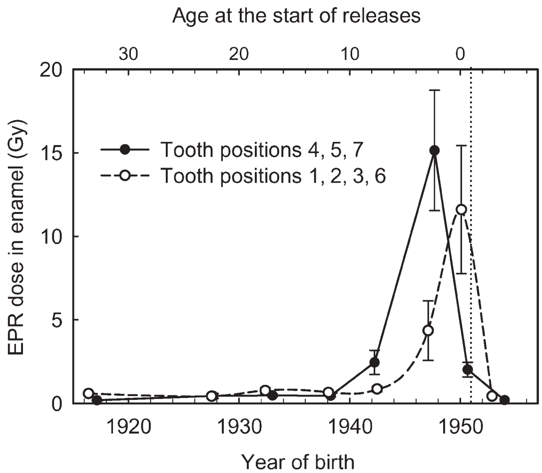

Figure 2. Age-dependent curves of average accumulated enamel doses measured with EPR in 1992–2006; the number of measurements is 420 for residents of upper- and mid- Techa. Dotted lines indicate the date of the beginning of releases; bars represent the standard error. Tooth positions correspond to the following tooth names: 1, 2- incisors; 3- canines; 4, 5- first and second premolars; 6, 7- first and second molars.

improved data and increased number of measurements confirm the past findings and clarify these dependences. In particular, the WBC data allowed detection of evident gender differences in the peak of ^{90}Sr retention in skeleton (Figure 1b). Since no gender differences are observed in tooth formation (there is a tendency for a more rapid formation in girls with a 0.3 year difference relative to boys[1]), combined TBC and EPR data on both genders are presented (Figures 1a and 2).

When incorporated in the teeth and the skeleton, ^{90}Sr starts eliminating at different rates, depending on various regulatory processes[5]. The analysis of correlation between TBC and WBC data was performed for residents of Muslyumovo of 1945–1949 years of birth, i.e. at the time when sharp increases in gender-dependent ^{90}Sr-body-burden were not yet observed. Table shows the correlations in the age groups of the residents of the same year of birth measured by TBC and WBC at the same time. The restriction to one year is explained by the fact that ^{90}Sr content in the teeth increases and ^{90}Sr in the skeleton decreases with the increase in the year of birth. As can be seen from the table, significant correlation (>90%) was found for all narrow age groups except the persons born in 1949, for whom sharp increases in ^{90}Sr contents in enamel are observed, and the results of WBC measurements are close to the detection limit. (It should be noted that for other age groups (older than 1945), the correlation was not found). The correlation between ^{90}Sr contents in child's teeth and body-burden (Table 1) confirms the appropriateness of the TBC data for reconstruction of ^{90}Sr intakes.

Table 1. Correlation between ^{90}Sr contents in anterior teeth and whole body (skeleton) obtained with TBC and WBC for Muslyumovo residents.

Birth year	Number of persons	Pearson correlation coefficient	*p*-value	Slope of linear regression
1945	21	0.38	0.09	1.24 ± 0.70
1946	33	0.45	0.008	1.16 ± 0.41
1947	35	0.75	<0.001	0.62 ± 0.09
1948	36	0.41	0.01	0.13 ± 0.05
1949	35	0.21	0.23	0.04 ± 0.03
1945–1949	160	0.04	>0.5	—

Estimates of ^{90}Sr dietary intakes for the Techa riverside residents

^{90}Sr content in the skeleton and teeth reflects the level of its intake. However, because the intake in the Techa riverside settlements was chronic with a complex schedule, application of a biokinetic model to the WBC measurements obtained many years after the intake cannot be used for the intake reconstruction, such inverse problem has a set of solutions. For tooth enamel this inverse problem is formulated simpler than for the skeleton because tooth enamel, unlike the skeleton, does not contain living cells, does not remodel during the life, the period of enamel formation is very short and independent of gender. To derive ^{90}Sr-intake function, the TBC data were related to two unknown functions: ^{90}Sr dietary intake and the Sr-transfer coefficient from the gastrointestinal tract (GIT) to enamel of the first permanent incisors. The equation was formulated in early 1970s[2], however, a proper solution was obtained recently[8], which proved its uniqueness and stability. The solution represents relative ^{90}Sr-intake function for 1950–1955 and relative Sr-transfer coefficient from GIT to enamel. The results of WBC measurements and data on ^{90}Sr specific activity in local foodstuffs obtained after 1956 allowed derivation of ^{90}Sr-intake function for residents of different settlements.

Figure 3 shows the new estimates for two Techa River settlements Metlino and Muslyumovo, the ^{90}Sr-intake estimates used in TRDS-2000 are presented for comparison. The total amounts of ^{90}Sr ingested during the period of releases (1950–1956) are close in new and old versions (about 2330 and 2250 kBq for Metlino; 3300 and 3100 kBq for

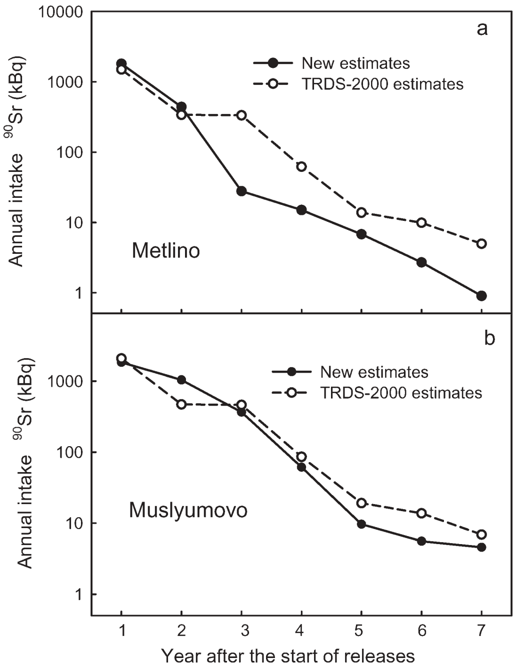

Figure 3. Comparison of new and TRDS-2000 estimates of ^{90}Sr diet intakes for residents of Metlino and Muslyumovo; the period of the most-sharp changes in the schedule of intake is considered to commence in August–September 1950.

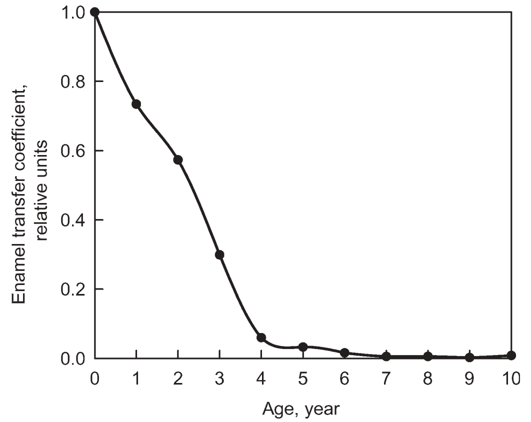

Figure 4. Relative values of Sr transfer coefficient from GIT to enamel of incisors depending on the age.

Muslyumovo). However, the annual ^{90}Sr-intakes for Muslyumovo have changed significantly, especially for 1951. For Metlino, a significant change in the dynamics of ^{90}Sr-intake is explained by the fact, that: early prohibition (in August 1951) to use the river water for drinking and early supply of the residents with clean water in this village were taken into account in ^{90}Sr-intake function for the first time. In Muslyumovo and other settlements such arrangements were not performed until 1953–1954.

Figure 4 illustrates the obtained relative values of transfer Sr coefficient from GIT to enamel of incisors. The maximum Sr transfer is observed during the first year of mineralisation, i.e. at the age of 0.5–1.5.

Application of EPR tooth measurements for Techa River dosimetric study

For the Techa River population the enamel-absorbed dose consists of three components[(4)]: background dose, dose due to ^{90}Sr incorporated in dental tissues (enamel and dentine) and the external dose. The contribution of these dose components differs in different age groups and depends on individual amount of ingested ^{90}Sr and the residence in specific settlements. (The latter condition deals with the fact that the main mass of gamma emitting radionuclides (the sources of external exposure) has subsided in the upper stream of the Techa River).

For young persons the main component of enamel dose is the dose from ^{90}Sr incorporated in the enamel and dentine, during the tooth growth and mineralisation. Two peaks, distinguished in the enamel doses (Figure 2), reflect the differences in the dates of mineralisation of specific teeth: incisors, canines and first molars (positions 1, 2, 3, 6), mainly develop at the age of 0.5–5 years, with the highest rate of crown growth and formation observed at the age of 1–2 years; premolars and molars (positions 4, 5, 7) develop with a delay of 2.5 years, that results in the shift of the peak of absorbed doses to the left. The data presented confirm and specify our results obtained earlier with a smaller number of measured teeth[(5)]. Taking into account the high enamel dose due to ^{90}Sr in the dental tissues the other two dose components (external and background doses) are indistinguishable. Only for persons whose enamel has been completely formed by the beginning of ^{90}Sr intake (mainly for persons born before 1940) all three dose components can be distinguished[(9)].

The average background doses for persons of 45–95 years old were estimated for people who did not live on the contaminated areas: 90 ± 24 mGy for premolars and molars and 154 ± 55 mGy for incisors. Preliminary calculations based on Monte Carlo simulation have shown that for Techa riverside residents born before 1940 (i.e. older than 45 years at the moment of EPR measurements), enamel doses from ^{90}Sr can amount to 150 mGy. The average values of external doses in Metlino and Muslyumovo were found to be 680 ± 200 mGy and 250 ± 60 mGy. So, for external dose assessment, the contribution of ^{90}Sr in accumulated dose in mature teeth should be considered as a hindrance, especially for people who lived in the mid-Techa. In order to enlarge the number of potential donors and to use the data on EPR measurements for persons with essential ^{90}Sr concentration in tooth tissues, additional studies on ^{90}Sr biokinetic in tooth tissues and elaboration of dosimetric model are performed under the European project on Southern Urals Radiation Risk Research (SOUL). The Sr biokinetic models are incomplete yet, however, some basic parameters such as ^{90}Sr elimination rates and relative transfer coefficient from GIT to enamel (Figure 4) were obtained for incisors.

CONCLUSIONS

(1) Correlations between ^{90}Sr content in the skeleton and tooth enamel are statistically significant for only narrow age groups (1945–1948 b.y.) due to distinctions in the tooth and skeleton mineral turnover. The correlation can be used for derivation of ^{90}Sr body-burden for persons measured with only one dosimetric method (TBC). In other age groups the correlation was not found.

(2) New values of ^{90}Sr intakes differ from the previous estimates used in TRDS-2000 both in dynamics and absolute values, mainly for 1951–1952.

(3) Detailed information on age- and gender-dependences in Sr turnover in mineralised tissues provide us with criteria for using tooth in retrospective dosimetry.

ACKNOWLEDGEMENTS

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Reference 9

About purified apple-pectin – a summaey from Prof Dr. med. Michel Fernex and a google reseach about Zosterin ultra

In France, purified pectin was developed by SANOFI for the treatment of chronic intoxication with heavy metals (Pb and Hg). Pectins are chemically related polysaccharides found in fruits, vegetables and algae. They are used for pastry and jam. Being poorly absorbed, and with a high affinity for heavy metals, pectin was commercialized for treating saturnism.

The Ministry of Health of the Russian Federation registered Zosterine-ultra®, a pectin preparation from seaweed, "as a food additive for removing heavy metals and radionuclides from the organism". It was considered as a defensive weapon for soldiers and for the civile population in case of nuclear conflict, during the cold war.

In Germany, an apple-pectin preparation was developed by Herbstreith & Fox (H&F), for the mentioned indications, but also for removing Sr-90 and Cs-137 from the organism. H&F showed that the urinary excretion of Pb and strontium (Sr-90), increases after several days of pectin intake. The urinary excretion of Sr-90, a widely spread beta emitter released by the burning reactor in Chernobyl, increased significantly after a prolonged intake of apple-pectin. This somewhat delayed phenomenon may be due to the enhanced absorption of pectin metabolites formed by the gut flora, which requires time to become able to break up the pectin-polysaccharide chain into absorbable fragments (www.herbstreith&fox.de ; updated 21.10.2005).

Korzum (9) showed that rats, fed with grain contaminated with Sr-90 and Cs-137, accumulate these radionuclides in their organisms. The addition of apple-pectin to their diet, blocked the uptake of radionuclides.

In the Ukraine, the German pectin-preparations and two others were put on the market with a Parlamentary Licence, for reducing the Cs-137 burden of radiocontaminated subjects. The reduction of the Cs-137 load is considered to be predominantly due to the adsorption of the metal ion in the gut lumen, then to its evacuation with feces. Elimination of heavy metals may also follow the absorption of fragments of the polysaccharide, metabolized by the gut flora. The urinary output of Sr-90 or lead, as shown by H&F was significantly increased, even more markedly during the second week of treatment, when compared with vegetal fibres alone.

Belrad (Belarus) developed a 16% apple-pectin preparation enriched with vitamins and essential elements (Vitapect®). The preparation was controlled by the Research laboratory of the European Commission, in Ispra, and accepted for field trials. It was clinically compared with the Ukrainian preparation, and proved to be at least as active in the elimination of Cs-137, and equally well tolerated.

A German-Belarussian placebo-controlled study, with the Juelich Nuclear Research Institute, on the impact of the Belrad preparation on the serum levels on essential metals in the blood of children (K, Zn, Fe, Cu), confirmed the safety demonstrated earlier by Gres & al., Minsk (10), showing the efficiency of a 16-day course in reducing the Cs-137 levels, and the stability or normalization of blood values for microelements (http://www.fz-juelich.de).

A double-blind, randomized, controlled trial in two groups of children, compared the Belrad preparation with placebo (8). It showed that the Belrad preparation eliminates Cs-137 from the organism in children receiving radiologically "clean" food. Clean food with placebo for 3 weeks reduced the Cs-137 burden by 14%; clean food with one spoon of the Belrad pectin-powder during meal reduced the Cs-137 burden by 63%, the difference is statistically significant ($p<0.01$).

Several reports have shown that children with a higher burden of Cs-137 require repeated apple-pectin courses of 3-4 weeks, at three to four months interval, until normalization. This is associated with an improved diet, which is part of the campaings conducted by Belrad. Other papers show furthermore, that the cardiovascular symptoms in these children are proportional to the Cs-137 burden.

A further publication showed that cardiovascular symptoms are proportional to the Cs-137 burden. A pectin course not only reduces significantly the Cs-137 burden, but also reduces clinical symptoms (5). This study shows the effectiveness and good tolerance of apple-pectin courses in children :

94 school children, from the same rural communities, were divided in 3 comparable groups ; they differ only by the Cs-137 burden in their organism: <5.0 Bq/kg BW ; 38 ±2.4 Bq/kg BW ; 122 ±18.5 Bq/kg BW.

A pediatrician, not knowing the radiametric findings, registered significantly more abnormal sounds at the auscultation of the children of the groups with moderate or high Cs-137 burden; ECG alterations were found in 87 % of the children of the group with 38 Bq/kg BW, and in 93 % of those with 122 Bq/kg BW. Only half of the children with <5.0 Bq/kg BW Cs-137 had anomalies of the ECG. Hypertension, defined as 20mmHg above the text-book upper limit for the age, measured after bending knees 10 times, was significantly increased in children with a moderate or high Cs-137 load. The arterial blood pressure was normal in
- 85 % of the children with Cs-137 <0.5 Bq/kg BW;
- 68 % of those with 38 Bq/kg BW; and in
- 40 % of those with 122 Bq/kg BW.

In the group with an average Cs-137 burden of 122 Bq/kg BW, significantly more complaints were expressed than in the other groups, 10 % showing signs of depression.

After a 16-day of apple-pectin course, the reduction of the ECG alterations was statistically significant in the children with a high burden of Cs-137. The ECG of children not receiving pectin (the Cs-137 levels being "normal" <0.5 Bq/kg BW), did not improve after 3 weeks (5).

Organ dose

"Organ doses" instead of whole body doses, are accepted for radioiodine in the thyropid gland. The same should be applied for incorporated Cs-137, where the dose has to be calculated separately for the target organs. For Cs-137, a <0.1 mSv whole body dose in a child, may correspond to >1.0 mSv in vital organs, such as pancreas, adrenals, thyroid, thymus and heart. In the nineties, many studies of the Gomel Institute of Pathology, have shown very different Cs-137 concentrations from organ to organ, measured at autopsy, with concentrations varying from 1 to 100, the highest levels being measured in endocrine glands and the thymus in small children (1).

The increased concentrations of Cs-137 in given organs, was associated with an increase of pathologies, especially in children who may suffer from diseases of elderly subjects. This "premature ageing„ includes cataract, cardiovascular diseases, diseases of the immune and endocrine systems, and cancer. Animal studies conducted in Gomel confirmed the autopsy findings (4). These experiments are being repeated in Western laboratories.

The myocardium and the thyroid gland was known to be target organs for radiocesium, in Western Europe in the sixties : Cs-131 was used to localize by scanning myocardial infarctions, as well as thyroid nodules.

In her medical thesis, G. Bandazhevskaya showed that with a Cs-137 burden over 20 Bq of Cs-137/kg BW, ECG alterations already occur in a high proportion of children.

Michel Fernex le 9 juin 2006

Algae pectine – usefull for the elimination of ^{137}Cs, ^{134}Cs, ^{90}Sr and Plutonium-isotopes of intern contaminated japanese people?

Japan people likes algae from the sea as food. Pectines may be contained in sea algae. We do not known, which algae are rich of pectin and which algae are eaten in Japan. But we know from a Russian medicament „Zosterin ultra* extracted and chemically treated from the Alga Zostera marina, the common eelgrass.

History of 'Zosterin Ultra'

In the 1950s, Prof. Melnikov (Russia) began the research on the extraction of pectin from marine plant named Eelgrass (Latin name: Zostera marina). Pectin was isolated from this raw material by various methods, but some major constituents of its structure appeared to be lost during the procedures. Later, at Pacific Institute of Bioorganic Chemistry (ТИБОХ), the group led by Prof. Ovodov developed a technology of isolation of Zosterin - pectin from Zostera, which allowed obtaining a relatively high quality product. That technology, however, was based on a chemical extraction principles that incurred significant costs of reagents and setting up the manufacture (compliance to environmental regulations). The pectin produced by the method mentioned has got the name "Zosterin Plus". Its content of low-molecular weight fractions did not exceed 8%.

Many specialists have been attracted by the idea of isolating pectin from eelgrass. It took about 40 years to develop a proper isolation and purification technology. Zosterin has been a subject of many research and clinical works, with the greatest contribution from the Pacific Institute of Bioorganic Chemistry, Vladivostok. Major results of the studies have been described in the monography "Zosterin" published by this Institute in 1997. However, further development of research in improving the manufacture technologies in this region has been unfortunately suspended. In the beginning of 1990s, those works were forcibly initiated in St. Petersburg by Drs. O.D. Dolgiy and S.K. Onikienko, both disciples of Prof. Brehman. Their works on revealing and characterising immunomodulating activity of vegetable and animal extracts became a basis for the development of an original technological process of manufacturing of food supplements. Further, the initiative group consisting of O.D. Dolgiy, M.V. Petrov, A.I. Pahomov and V.P. Ognev. That team, based on all findings obtained before, developed a new technology of isolation and purification of pectin that got the name of "Zosterin Ultra". Then a Joint stock Company "Bentos" was created, with the Director General being M.V. Petrov, his Director of Research being O.V. Dolgiy, the Vice Director being A.I. Pahomov and the Head of Chemical laboratory - M.Y. Turkina. A group of experts from Research Institute for High Frequency Currents (St. Petersburg) has begun developing laboratory equipment for the extraction of the pectin. For research and promotion of Zosterin Ultra, Mai Company Ltd. was founded, which was directed by S.V. Shpynov and A.S. Zelenko and employed Dr. S.L. Burova, a consultant physician. This company initiated clinical studies of Zosterin Ultra in some research medical institutions. Since then, Zosterin Ultra has got excellent references from physicians of St. Petersburg. After a three-year cooperation, Joint stock company "Bentos" and "Mai Ltd". merged forming a new Joint stock company named "Akvamir" that started the construction of an industrial manufacture of Zosterin Ultra. M.V. Petrov became its Director General. In 1999, the company was awarded the Diploma of IV International Exhibition and Congress "High technologies. Innovations. Investments" for the development of pectin Zosterin Ultra from the marine herb. In 2000, Zosterin Ultra became a formal winner of the State competition of new technologies. In 2001, Zosterin Ultra project became a leader of the 500 projects competing, and the product was awarded a Diploma and the I.I. Mechnikov`s Gold medal of the Russian Academy of Natural Sciences "For the practical contribution to the strengthening of the nation`s health". At the same time, the project won the formal competition at the Ministry of the Nuclear Industry. It was granted two interest-free State credits for the construction in St. Petersburg of a large-scale industrial manufacture. In 2002, formal "Guidelines for the application of pectin "Zosterin Ultra" in the treatment and prevention purposes at the enterprises of a nuclear fuel cycle and the territories polluted with radioactive compounds" coded MP-12.07-02 were issued by the Ministry of Health. State Research Institute of Radiation Hygiene of the Ministry of Health confirmed and approved the data on accelerated elimination of plutonium and other heavy metals from the body by Zosterin Ultra (statement of the expert committee N 111/2, dated 24.10.02).

Reference 10

Reducing the 137Cs-load in the organism of "Chernobyl" children with apple-pectin

V. B. Nesterenko, A. V. Nesterenko, V. I. Babenko, T. V. Yerkovich, I. V. Babenko

Summary

As a complement of standard radioprotective measures, apple-pectin preparations are given, especially in the Ukraine, to reduce the 137Cs uptake in the organism of children.

The question has been raised: is oral pectin also useful when children receive radiologically clean food, or does this polysaccharide only act in binding 137Cs in the gut, blocking its intestinal absorption? In this case, pectin would be useless if radiologically clean food could be given.

The study was a randomised, double blind placebo-controlled trial comparing the efficacy of a dry and milled apple-extract containing 15–16% pectin with a similar placebo-powder, in 64 children originating from the same group of contaminated villages of the Gomel oblast. The average 137Cs load was of about 30 Bq/kg bodyweight (BW). The trial was conducted during the simultaneous one-month stay in the sanatorium Silver Spring. In this clean radiological environment only radiologically "clean" food is given to the children.

The average reduction of the 137Cs levels in children receiving oral pectin powder was 62.6%, the reduction with "clean" food and placebo was 13.9%, the difference being statistically significant ($p < 0.01$).

The reduction of the 137Cs load is medically relevant, as no child in the placebo group reached values below 20 Bq/kg BW (which is considered by Bandazhevsky as potentially associated with specific pathological tissue damages), with an average value of 25.8 ± 0.8 Bq/kg.

The highest value in the apple-pectin group was 15.4 Bq/kg, the average value being 11.3 ± 0.6 Bq/kg BW.

Key words: "Chernobyl" children; reduction of the 137Cs load in the organism; controlled trial; oral Apple-Pectin vs. Placebo

Introduction

The radioactive fallout after the explosion of the Chernobyl power plant in the Ukraine, (April 26, 1986) exposed 23% of the territory of the neighbouring country, Belarus, to a 137Cs contamination of over 1 Curie per square km (>37 000 Bq/m^2). The agricultural production was stopped on 264 000 hectares. About 2 million people, among them 500 000 children, live in this area, contaminated principally with 137Cs and 90Sr [1].

The mobile teams of the Institute for radioprotection BELRAD measured the 137Cs load in the children's organism. So far 160 000 were checked: the 137Cs levels of 70 to 90% of the children of these regions exceeded 15–20 Bq/kg bodyweight (BW). In many villages the 137Cs levels reached 200–400 Bq/kg BW, the highest values being measured in the Narovlya district with 6700–7300 Bq/kg BW.

At the Medical State Institute of Gomel, under the direction of Prof. Yuri Bandazhevsky, studies were conducted during nine years, showing that the chronic accumulation of 137Cs in different organs contributed to progressive deterioration of health [2–3].

BELRAD created information centres for the rural population, equipped with spectrometers for measuring the 137Cs contamination of foodstuffs, milk and fodder, free of charge; 320 000 such samples were analysed. These teaching and informing efforts, as well as the radiologically "clean" food provided by the government twice a day to schoolchildren since kindergarten, also free of charge, did not lead to a satisfactory reduction of the 137Cs load in the organism of the children.

Therefore, we started to study pectin, a polysaccharide found in different sorts of fruits, and generally used in Europe for the preparation of sweets and jam. Purified pectin is also prescribed as an oral adsorbent for heavy metal (lead and mercury) intoxication. This medicament was initially developed by Sanofi (France) for the treatment of saturnism.

Since ten years, different pectin preparations based on milled dry-apple leftovers after pressing, are given orally to children living in radio-contaminated areas of the Ukraine, for reducing the radiocaesium load in their organisms. Korsum [4]

This trial was sponsered by "Enfants de Tchernobyl Belarus", F-68480 Biederthal.

showed that apple-pectin given to rats, together with radiocontaminated food, reduced significantly the uptake of 137Cs and strontium (Sr90).

In Belarus, the safety and efficacy of apple-pectin preparations, as well as their capacity to eliminate heavy metals from the organism was studied by Gres et al. [5].

Aim of the study

The objective of this study was to verify if pectin is still active in children when radiologically clean food is given, because the mode of action of this adsorbent is the binding of heavy metals (including 137Cs) in the intestinal lumen, the complex being then eliminated with the faeces.

Method

We planned to compare the percentages of the incorporated 137Cs eliminated from the organisms of two groups of children, all originating from the same rural area of the Gomel oblast, during their one-month stay in the Sanatorium "Silver Spring". In this radiologically "clean" environment all children received exclusively "clean" food.

Besides radiologically clean food, one group received one teaspoon of apple-pectin powder (5 g) diluted in water twice a day, at meals, for three weeks. The other group received the same food as well as a similar powder but containing no pectin, i.e. a placebo, for the same period of time.

All families were informed about the three weeks trial, which included a radiometric measurement before and after the trial. The children gave an oral informed consent, knowing that they could quit the trial any time, without any justification. All mothers gave a written informed consent, being told that all children from the placebo group would receive a box of pectin powder when leaving the sanatorium.

Sixty-four children accepted to participate in the study. Based on a randomisation table, 32 children received a box containing a 15–16% apple-pectin powder, and 32 a placebo powder. The key for the preparation given was kept by a member of the Ethical Committee, to be opened after all 137Cs measurements would be registered, and the complaints or clinical findings would be written down in the individual medical questionnaires.

The results compared the tolerance and acceptabil-

Table 1

Double-blind comparison of the 137Cs whole-body count (Bq/kg) of schoolchildren, before and after a 3-week cure with simultaneous one-month stay in a sanatorium, with a radiologically clean environment and "clean" food. Comparison of the 137Cs whole-body count (Bq/kg bodyweight) in children before and after a 3 week pectine intake.

Name & Year of birth	Sex	137Cs whole-body count before pectine intake, Bq/kg	137Cs whole-body count after pectine intake, Bq/kg
A.A.N., 1993	F	40.2	15.3
B.I.S., 1992	F	36.0	12.6
B.Ju.E., 1990	F	34.9	13.9
G.A.N., 1993	F	34.5	15.4
G.E.V., 1993	M	34.0	14.1
G.E.V., 1990	F	33.9	15.3
G.N.O., 1992	M	32.5	11.7
G.V.V., 1991	F	32.5	12.7
G.M.N., 1992	F	31.8	12.2
G.V.N., 1990	F	31.3	13.9
Z.K.V., 1991	F	31.1	14.7
I.Ya.A., 1990	M	30.9	12.6
K.A.S., 1994	M	30.1	11.9
K.A.S., 1991	M	29.5	5.0
K.I.L., 1990	M	29.2	12.4
K.V.A., 1990	M	29.0	5.0
K.V.E., 1993	M	28.9	13.2
L.A.S., 1993	F	28.2	5.0
M.YA.N., 1992	F	28.1	5.0
M.R.S., 1992	M	27.9	11.6
P.E.M., 1993	M	27.8	11.9
S.E.F., 1993	F	26.2	12.3
T.A.V., 1993	F	25.8	10.2
T.V.S., 1991	M	25.8	11.0
F.D.A., 1992	M	25.6	9.2
Ch.D.V., 1993	M	25.4	10.0
Sh.R.A., 1990	M	25.3	11.9
Yu.A.L., 1993	F	25.3	5.0
Mean value		30.1 ± 0.7	11.3 ± 0.6

ity, as well as the difference in the percentage of reduction of the 137Cs load during the two courses, with a statistical analysis of each group.

Measurement of the whole body count of 137Cs

The radiometric measurements were performed by a team of BELRAD equipped with a mobile anthropogammametre "Screener-3M" of Ukrainian origin, with electronic registration of the findings. (The seven mobile spectrometres from BELRAD were cross-checked with two corresponding mobile spectrometres of the Research Centre Juelich "Canbera-Fastscan-whole BC", Germany. The difference did not exceed 11%. A second comparative control showed that differences in repeated examinations of a great number of children did not exceed 7%). The scientific accuracy of the measurements is also guaranteed by the annual, compulsory State Examination of the equipment.

Results

The key was opened by a member of the Ethical Committee, after the information was registered.

All 64 children completed the cure. The two preparations were equally well accepted and tolerated. Three families had to leave the sanatorium before the radiological control, so that four children missed this control. Two children (one of each group) refused to have a second 3-minute radiometric examination, without giving any reason.

Table 2
The mean decrease was 62.6% in the pectin-treated group. Comparison of the 137Cs whole-body count (Bq/kg bodyweight) in children before and after a 3 week placebo intake.

Name & Year of birth	Sex	137Cs whole-body count before placebo intake, Bq/kg	137Cs whole-body count after placebo intake, Bq/kg
A.R.V., 1992	M	48.4	41.8
A.D.E., 1990	M	37.0	31.2
A.N.O., 1990	F	36.2	31.3
B.V.G., 1992	M	35.2	27.5
V.A.V., 1994	M	34.7	29.0
G.D.A., 1993	M	34.4	30.5
G.A.S., 1993	M	33.9	28.0
G.V.V., 1993	M	33.5	29.2
G.V.S., 1993	M	32.5	27.5
Z.M.N., 1994	F	31.2	27.5
I.K.A., 1991	F	30.5	28.5
K.V.S., 1993	F	30.3	25.4
K.E.M., 1990	F	29.5	25.2
K.N.V., 1990	F	28.6	24.9
K.Ya.A., 1992	F	28.4	23.6
L.K.A., 1991	F	28.1	24.2
M.Yu.A., 1994	F	28.1	23.2
M.E.A., 1992	M	28.0	26.3
P.E.A., 1991	M	27.5	25.6
P.Ya.V., 1990	F	27.2	20.1
R.S.P., 1991	M	26.5	22.5
S.I.A., 1992	M	26.3	24.1
S.E.M., 1994	F	26.1	23.7
T.A.A., 1992	M	25.9	21.6
T.E.S., 1992	F	25.7	21.9
Kh.S.I., 1993	F	25.5	22.3
Kh.T.F., 1993	F	25.5	23.9
Sh.Ya.N., 1992	F	25.4	21.1
Yu.A.V., 1992	M	25.3	22.8
Z.I.S., 1993	M	24.8	20.0
Mean value		30.0 ± 0.9	25.8 ± 0.8

The mean decrease was 13.9% in the placebo-treated group. The difference in the decrease is statistically significant p <0.01. The initial 137Cs values are identical in both groups. The average decrease of the 137Cs load was 62.6% in the Pectin-group. The average decrease of the 137Cs load was 13.9% in the placebo group. The difference was statistically significant, p <001.

Therefore, the findings are based on 58 measurements. Table 1 shows the 137Cs load measured before and after the cures in each individual child, and the average levels in the two groups.

The initial average values for 137Cs were just above 30 Bq/kg bodyweight (BW) in both groups: 30.0 and 30.1 Bq of 137Cs/kg BW respectively.

After the cure, there was a drop of the 137Cs load in all tested children. However, no child from the placebo group reached values for 137Cs below 20 Bq/kg BW, the average value being 25.8 ± 0.8 Bq/kg BW, i.e. a reduction of 13.9% of the 137Cs load.

After the 3-week pectin intake, the highest value in a child of the group receiving apple-pectin was 15.4 Bq of 137Cs/kg BW. As values below 5.0 Bq/kg BW are no more within the limits of precise measurement, these findings were taken as being 5.0 Bq/kg BW. The average values in this group is 11.3 ± 0.6 Bq/kg BW, corresponding to a reduction of 62.6% of the 137Cs load.

The difference between the two groups is statistically significant ($p < 0.01$).

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Reference 11

Peer reviewed article

A national cancer registry to assess trends after the Chernobyl accident

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Summary

The National Cancer Registry has been operational in the Republic of Belarus since 1973: information on all new cases of malignant tumours is registered. The data are kept in a computer database and used for assessing the oncological status of the population, and for epidemiological studies. We compared findings before the Chernobyl accident of April 26, 1986 (Chernobyl) and findings between 1990 and 2000. The overall comparison on the changes in the incidence of cancer morbidity in Belarus is presented. The increase is statistically significant for all regions, but significantly greater in the most chronically radiation-contaminated region: the Gomel oblast.

The paper presents a comparative analysis of the incidence of cancer morbidity in the population of two regions of Belarus, selected for the greatest difference in their radioactive contamination following Chernobyl. The highest contamination occurred in the Gomel region and is mainly due to high levels of radiocaesium (^{137}Cs) in the soil and in the alimentary chain, especially in rural areas. A relatively low radioactive fallout was noticed in the Vitebsk region, considered here as the "control" area. We compare the situation before and after Chernobyl in the two regions. The overall cancer morbidity rate in all organs including colon, urinary bladder and thyroid, was significantly higher in the Gomel region than in Vitebsk.

In populations living in two areas with high ^{137}Cs contamination (oblast of Gomel and Mogilev), the peak incidence rates of breast cancer were already reached between the ages of 45–49 years, 15 years earlier than in the Vitebsk region.

Belarussian "liquidators" who were mobilised to clean up the most contaminated territory and build the sarcophagus around the destroyed atomic plant, received the highest radiation doses. They had a significant excess of incidence of cancers of colon, urinary bladder, and thyroid gland, when compared with a corresponding adult population of the Vitebsk region.

The Relative Risk (RR) of lung cancer among "liquidators" in 1997–2000 significantly exceeded 1, while in the control population it remained stable.

Key words: incidence of different solid cancers; Chernobyl accident; liquidators

Introduction

The Chernobyl accident (Chernobyl) resulted in negative social, economic and medical effects. Radioactive iodine and over hundred other radioisotopes were thrown out in the atmosphere, the fallout covered the whole territory of Belarus.

During the first weeks, ^{131}iodine played the leading role in the exposure of the population. Only a northern part of the country (mostly in the Vitebsk region) was relatively "clean". The rest of the territory was contaminated with 5 and more curies (Ci)/km^2. The greater part of the Gomel region, and parts of the Mogilev and Brest regions, were contaminated with more than 50 Ci/km^2 of ^{131}I. In some areas of the Gomel region, the levels of ^{131}I exceeded 300 Ci/km^2 [1, 2].

Initially, radio-iodine was responsible for high doses to the thyroid and later considered as responsible for thyroid cancer and other thyroid diseases [3, 4]. Stable iodine prophylaxis started 10 days after the accident and was useless since by that time the thyroid had already taken up huge amounts of ^{131}I.

Due to the Chernobyl accident 43500 square kilometers of Belarus were contaminated by long-lived isotopes of caesium (Cs), strontium (Sr) and transuranians. 2.1 million inhabitants (23%) of Belarus lived in the territory with ^{137}Cs level of more then 40 kBq/m^2. 7.9% of the national territory had ^{137}Cs levels exceeding 185 kBq/m^2 (5 Ci/km^2). More than 90% of such territories are located in the Gomel and Mogilev regions. According to the assessment, when the level of the soil contamination reached 100 kBq/m^2 (2.7 Ci/km^2), the average annual effective dose is 0.1–0.2 mSv [5, 6].

No financial support declared.

In order to protect populations living in the most contaminated areas 135'000 individuals were relocated. About 120'000 citizens of Belarus were mobilised to clean up and decontaminate the area around the nuclear power plant and the 30 km zone of exclusion around Chernobyl. These workers, so-called liquidators, received the highest exposure doses. Due to unavailability of equipment, it was not possible to measure real exposure doses. Dose estimates are still a point of discussion among specialists. This fact makes it impossible to accurately estimate the prognosis of later stochastic effects of ionizing exposure and radiation risk.

According to some estimates, (including UNSCEAR 2000) up to 90% of the cumulative dose was received during the period of 1986–1995. The average individual doses received in 1986–1995 by the population living on the territories with a contamination of 37–185 kBq/m^2 (1–5 Ci/km^2) were 3.9 mSv; on the territories with 185–555 kBq/m^2 (5–15 Ci/km^2) the doses were 18.7 mSv, and with more than 555 kBq/m^2 (>15 Ci/km^2): 47 mSv. At present, the exposure dose is mainly due to internal irradiation by incorporated radionuclides, a minor proportion being due to external exposure. An excess over the permissible annual doses affects mostly the rural population [4, 6].

Materials and methods

Data of the National Cancer Registry and Registry of the subjects affected by the Chernobyl accident served as basis for this study. In 1973, the database for malignant cancers was established in Belarus, where the information on each newly diagnosed case of malignant tumour was registered. Special record forms called "Dispensary follow-up records" served as sources of information for establishing the database. These forms were filled-in and coded in the different oncology units ("dispensaries") in Belarus. At the end of each year they were sent to the Republican Oncology Institute for computer processing. Up to 1985, family names of patients were not recorded on this computer (PC) database, but the individual number of the patient was [7].

There are 12 oncology units in Belarus: 1–3 in each region. These units provide data from all oncology patients and treatment for 80% of them. In accordance with the legislation, every hospital and out-patient department has to present information of newly diagnosed cases to the local oncology unit. In each area an oncologist performs a survey of the patients, notifying the units. Such a system allows strict control over all cases of malignant neoplasia.

The majority of oncology patients in Belarus are examined and treated in oncology units or at the Republican Institute for Oncology and Medical Radiology. All information introduced into the PC memory is taken from primary medical records of the oncology units. Details from medical documents and notifications from other medical institutions where the diagnosis of malignant tumour was made (and treatment carried out) are sent to the oncology unit. Pathologists also send the oncology unit information about cases of malignant tumours confirmed at autopsy.

Thus, comprehensive information is continuously compiled which makes it possible to undertake epidemiological studies among groups of populations in Belarus affected by Chernobyl.

In 1985–1989, a PC control system of oncology units, including the follow-up of cancer patients was gradually established. The main features of the new system are:

- the use of full ICD-9 and –10 and ICD-0–2 for coding malignant tumours (site and morphological structure)
- built-in an algorithms for quality control of the information (agreement between tumour site, morphology, sex and age), developed based on the recommendations of the International Agency for Research of Cancer (IARC).

A national registry for people affected by Chernobyl collects personal data from liquidators, or subjects relocated from the contaminated areas, and of persons still living in contaminated territories. Unification of the system of the cancer registry and of the Chernobyl registry allows assessment of cancer incidence rates in these populations.

Statistical evaluation

In order to study the morbidity rates of groups according to the radioactive risk, the Vitebsk region was chosen as a control, due to its lowest chronic contamination level in Belarus. The population of this region was least affected by Chernobyl; there are only few persons living in the Vitebsk region, who were resettled from the Chernobyl areas. When analysing the morbidity rate in the control group, all cancer cases diagnosed among people who were resettled in or evacuated to Vitebsk, as well as in liquidators were excluded from the study.

Since age and sex distribution in the studied groups often differed from that of the controls, the comparative analysis of the morbidity rates was carried out using standardised indices, by the method of age-standardisation technique. When comparing the incidence in different regions of the country standardised indices calculated for age groups with 5-year intervals from 0 to 85 and older were used: for liquidators aged 20–85 years and more. TASR (truncated age-standardised rate), was also used for the estimation of thyroid cancer morbidity in the adult population, from the age of 30–85 years and older (excluding children who became adults after 1986).

While comparing the mean incidence indices for a number of years, mean of raw variation and standard errors of mean values were calculated. A significant difference in mean values was estimated using the Student criterion.

While estimating relative risk (RR) values, the liquidators, ie, the "exposed group" was compared with the "non-exposed group" from the corresponding population of the Vitebsk region, selected by using TASR technique for the analysis. Changes in the morbidity rates were assessed, using trend models [8, 10]. Age indices of breast cancer incidence were calculated for the female population of corresponding control regions.

Cancer morbidity in the population of Belarus

Though a great number of publications after Chernobyl deal with thyroid cancer in children, this well recognised malignant solid tumour does not represent more then 0.4% of the total of the cancers described here.

Table 1 shows mean standardised morbidity data and linear regression coefficients for 2 periods of time (1976–1985 and 1990–2000). In the whole republic, the average morbidity rates for all cancers increased by 39.8%, which is statistically significant (from 155.9 to 217.9 per 100'000 inhabitants).

A statistically significant increase in the morbidity was observed in all regions of Belarus, but it was most pronounced in the Gomel region, where it increased by 55.9%. From 1976–1985, the morbidity rate in the Gomel region was lower than the mean republican level. In 1990–2000, it exceeded the republican level, due to the more rapid growth in the morbidity rates as compared with other regions.

The largest increase in the regression coefficient is noted in the Gomel region: from 2.79 in 1976–1985 to 5.8 in 1990–2000. In other regions, no significant increase in the regression coefficient was calculated (Table 1).

In 1990–2000, a significant increase in the regression coefficient is recorded for the cancer of colon, urinary bladder and thyroid. In the last decade, the incidence of lung cancer decreased markedly in all regions of Belarus. At the same time, differences in the regression indices for lung cancers in Gomel region, before and after Chernobyl, are less pronounced when compared with the other regions of Belarus. In other words, in Gomel region, which is most contaminated with radionuclide, there are factors preventing a decrease of the incidence of lung cancer.

Age specific distribution of breast cancer incidence in Belarusian females living in the Gomel, Mogilev and Vitebsk regions have shown that the peak incidence rates of breast cancers in females from Gomel and Mogilev regions were reached at the age of 45–49 years, 15 years earlier than in the Vitebsk region.

The curves of the incidence depending on age, show a considerable shift towards younger age groups, which is especially marked for females living in villages of contaminated regions as compared with urban populations. But the global average incidence rate of breast cancer for the Gomel, Mogilev and Vitebsk regions did not show statistically significant increases in this period.

In the Gomel region, the collective cumulative radiological doses in the rural population are twice as high as in the urban population. The collective dose received by the rural population from 1986 to 1994 exceeds twice the dose of the urban population of the Gomel region ie, 7349 and 3656 men-Sv, respectively [4, 9].

In the population of the Gomel region, living in areas with levels of ^{137}Cs over 555kBq/m^2, an important increase in the cancer morbidity was recorded. The higher average level from 1993 to 2002 for digestive and respiratory organs is statistically significant. When comparing this group with populations living in regions with the lowest level of contamination, the average cancer incidence rates for the groups of digestive organs were respectively: 141.5 ± 8.4 and 104.7 ± 10.1, $p < 0.05$; for respiratory organs: 83.7 ± 6.0 and 53.1 ± 5.3.

The incidence of thyroid cancer

The increase in the incidence of thyroid cancer among children is indisputable. The unparalleled increase of more than 100×, is considered to be due to radioactive iodine in the first weeks following Chernobyl [3, 11].

The incidence in adults also increased, however, for a long time this increase gave rise to very little scientific interest. Before Chernobyl, thyroid cancer was a rather rare malignant disease among adults in Belarus. After 1990, the incidence of thyroid cancer sharply increased and reached the highest world rates recorded in recent years.

In 1980 the standardised index of thyroid cancer incidence among the adult population older than 30 years of age was 1.24 per 100'000. In 1990 this index was 1.96, and in 2000 it reached 5.67. Children whose age at the time of the accident was 0–14 years, moved up to the age group 15–29 years by 2000, and therefore were not included in the group of adults. Among the liquidators the standardised index of incidence for the period of 1993–2000 was 24.4 per 100'000.

Incidence of cancer morbidity in liquidators

Among liquidators, a significant increase in cancer morbidity was recorded during the period under study. The cancer incidence is significantly higher ($p < 0.05$), when compared with the adult population (more than 20 years of age) in the Vitebsk region, using the truncated standardised indices (TASR), from 1993–2000.

Table 2 shows that the global cancer morbidity rate in all sites, including the cancer of colon and urinary bladder, was significantly higher in liquidators than in the control group of the same age and sex. The increase in incidence is based on average values of annual incidence increase and linear regression rate.

Average annual excess rates of cancers in all sites in liquidators was 5.5%, which is significantly higher than in the adult population of the Vitebsk region, where it was 1.5% ($p < 0.05$). The incidence of colon cancer accounted for 9.4% in liquidators, and 3.2% in the adult population of Vitebsk region ($p < 0.05$), kidney cancer: 8.0% and 6.5% ($p < 0.05$), urinary bladder cancer: 6.5% and 3.8% ($p < 0.05$), respectively.

To estimate the variation in the increase in incidence, trend models were used. The regression coefficient analysis (a) of the morbidity changes showed a marked growing trend for the incidence of colon cancer (a = 3.4 ± 1.1) among liquidators, as compared with the adult population living in the Vitebsk region (a = 0.47 ± 0.2, $p < 0.05$), lung cancer (a = 6.7 ± 2.3, and 1.3 ± 1.5, $p < 0.05$), bladder cancer (a = 1.2 ± 0.4 and 0.25 ± 0.1, $p < 0.05$), as well as globally for all cancer sites (a = 25.2 ± 7.6 and 7.4 ± 3.2, $p < 0.05$) respectively.

Table 1

Average incidence/year for all types of cancers (in 100'000 Inhabitants, based on standardised indices, world standard). Comparison in 7 regions of Belarus, and globally in the whole country.

Region	Average incidence and standard error*		p	Regression rate and standard error*		p
	1976–1985	1990–2000		1976–1985	1990–2000	
Brest	150.1 ± 2.81	199.5 ± 2.6	<0,001	2.80 ± 0.26	2.30 ± 0.40	>0.05
Vitebsk	158.2 ± 3.24	217.9 ± 3.5	<0,001	2.60 ± 0.63	2.90 ± 0.67	>0.05
Gomel	147.5 ± 2.52	224.6 ± 6.3	<0,001	2.79 ± 0.24	5.80 ± 0.86	<0.01
Grodno	143.8 ± 3.11	207.2 ± 4.2	<0,001	2.72 ± 0.71	3.52 ± 0.79	>0.05
Minsk	145.3 ± 3.26	216.6 ± 3.9	<0,001	3.01 ± 0.48	2.77 ± 0.91	>0.05
Mogilev	166.4 ± 3.98	219.6 ± 3.1	<0,01	4.04 ± 0.45	2.80 ± 0.46	>0.05
Minsk city	223.5 ± 5.72	263.7 ± 1.76	<0,001	5.51 ± 0.25	–0.08 ± 0.58	<0.001
Belarus	155.9 ± 3.80	217.9 ± 3.4	<0,001	3.76 ± 0.32	3.15 ± 0,44	>0.05

* The regression rate (± the standard error in observation periods) is compared before the Chernobyl accident (1976–1985) and after 4 to 14 years (1990–2000). It includes all the residents in each region and the global population of Belarus.

Table 2

Incidence of different cancers among male liquidators during 1993–2000, compared with the control group of adults (Vitebsk) (TASR m per 100'000 of the population[1]).

Site	ICD IX code	Vitebsk region	liquidators
All sites	140–208	361.2 ± 6.4*	400.8 ± 7.7
Stomach	151	44.4 ± 1.2	42.1 ± 2.5
Colon	153	16.1 ± 0.6*	21.6 ± 1.8
Rectum	154	17.9 ± 0.6	19.1 ± 1.7
Lung	162	53.9 ± 1.6	56.9 ± 2.9
Skin	173	33.0 ± 1.8	28.9 ± 2.1
Breast	174	57.3 ± 0.9	59.8 ± 6.7
Urinary bladder	188	10.4 ± 0.4*	16.9 ± 1.6
Kidney	189	13.0 ± 0.9	16.2 ± 1.6

1 TASR – truncated age-standardised rate for aged 20–85 years and older. Excluding liquidators and evacuated people from Vitebsk region.

* significant differences: all sites: $p < 0.001$; colon: $p < 0.01$; urinary bladder: $p < 0.001$.

Table 3

Relative risk (RR) in the incidence of cancer of liquidators from 1997 to 2000, compared with the adults of the control group (Vitebsk). (TASR m per 100'000 of the population[1]).

Site	expected (control region)	observed (liquidators)	RR	95 % confidential level	
All sites	373.3	449.3	1.20*	1.14	1.27
Stomach	41.7	44.9	1.08	0.92	1.26
Colon	17.0	22.3	1.31*	1.03	1.67
Rectum	19.0	18.4	0.97	0.77	1.23
Lung	52.4	67.3	1.28*	1.13	1.46
Breast (female)	58.6	61.3	1.05	0.81	1.35
Urinary bladder	10.9	17.0	1.55*	1.21	1.99
Kidney	14.8	17.9	1.21	0.97	1.50

* significant differences for all sites, colon, lung and urinary bladder.

1 TASR: truncated age-standardised rate for aged 20–85 years and older.

For other forms of cancer, no significant difference was found when compared with the control region. Among females, no statistically significant increase was recorded in cancer sites under study. The cohort of female liquidators from Belarus was only 5500.

The evolution of the incidence of stomach cancer among liquidators compared to the adult population in Vitebsk region, showed a contrary trend, which was not statistically significant (regression coefficient was 2.6 ± 1.6 among the liquidators and –1.03 ± 0.4 in the control group, $p > 0.05$). An statistically significant increased incidence in lung cancer was observed in liquidators. In the population of the control group, the incidence of lung cancer slightly decreased (regression coefficient was 6.1 ± 2.1 and –0.73 ± 0.7 accordingly, $p < 0.05$).

Among liquidators, living in areas with the levels of contamination of ^{137}Cs higher than 555 kBq/m^2, the mean incidence of respiratory tract cancer (larynx, trachea, bronchi and lung) was 80.1 ± 16.4, in 1993–2002, compared to 44.7 ± 7.0 per 100'000 liquidators living in regions with a contamination level equal to or below 185 kBk/m^2.

Relative Risk (RR) values were studied separately during the two periods of time (1993–1996, and 1997–2000). From 1993 to 1996 no statistically significant excess was found in cancer sites under study. From 1997 to 2000 RR significantly exceeded 1 for colon cancer, lung cancer and bladder cancer, as well as globally for all forms of solid cancers (Table 3).

Discussion

When comparing populations living in highly radio-contaminated regions with those living in "clean" regions, significant differences are noted in the incidence of cancer morbidity. The collective dose in the rural population is twice as high as in the urban population In even more irradiated subjects, such as liquidators. The increase of the cancer morbidity is even greater.

Exposure to radioactive iodine is apparently responsible for the increase in thyroid cancer in the adult population. A significant increase in adults has been recorded since 1991. The data of 1993–2000 also show an increase of this disease in liquidators.

Although a great number of publications after Chernobyl deal with thyroid cancer in children, this well recognised malignant solid tumour does not represent more than 0.4% of the total of cancers described here. The increased incidence of thyroid cancers among adults did not arouse scientific interest.

A significant increase in the incidence of cancer morbidity of colon, lung, urinary bladder and thyroid gland, as well as cancers of all sites, was observed in the population of the contaminated areas. This increase is significant in inhabitants of the most contaminated Gomel region and in liquidators. The RR for cancers in liquidators significantly increased only in recent years (1997–2000) ie, after a 12–15 year latent period. Significantly higher RR during these years was found for cancers of colon, lung urinary bladder and globally, for all sites (table 3). A significantly higher incidence of thyroid cancer was also recorded in liquidators. In the liquidators with the highest dose exposure for periods of one to several months close to Chernobyl, there is a significant increase of the incidence of the morbidity for different cancers, more marked among those who worked there for a longer a period of time.

In the adult population of the Vitebsk region, and in the global population of Belarus, there is a trend towards a decrease of the incidence of stomach cancers, whereas among the liquidators, there is an opposite trend: the increase may, in the near future, become statistically significant.

The peak incidence rates of the breast cancer was reached 15 years earlier in women of the Gomel and Mogilev regions as compared with women of the Vitebsk region. It is extremely difficult to estimate the tobacco consumption in Belarus. Therefore, it is impossible to determine if this plays a role besides radiation in the increase of lung cancers in liquidators. The higher incidence in the morbidity of cancer in the liquidators who had received the greatest doses during their work, constitutes a significantly higher risk when they live in the radio-contaminated areas of the Gomel region. In the Gomel region, the tobacco consumption had no reason to be higher among liquidators, than in other territories of Belarus.

The scientific community reads a lot about the increase of the thyroid cancer in children, considered to be a consequence of the exposure to radioactive iodine. In the adult population a 5-fold increase of incidence of this cancer was found, but this fact has not yet been reflected in documents of the IAEA, and the UNSCEAR, although we have published data showing the increased incidence in thyroid cancer in adults following Chernobyl.

According to published data on the effects of the A-bombs of Hiroshima and Nagasaki, there was a significant increase in the relative risk for cancer of colon, urinary bladder, lung, stomach and some other neoplasms, 10 to 20 years after exposure [12], showing the correlation between these tumours and ionizing radiation. Therefore, the corresponding findings after Chernobyl are not surprising.

The groups of highest risk are populations continuing to live in radio-contaminated territories and those consuming contaminated food since 1986.

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Reference 12

Peer reviewed article

Relationship between Caesium (^{137}Cs) load, cardiovascular symptoms, and source of food in "Chernobyl" children – preliminary observations after intake of oral apple pectin

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Summary

Seventeen years after the nuclear power accident at Chernobyl, most of the radio-contamination among the population of Southern Belarus is caused by incorporation of long-lived radioisotopes. The varying levels of ^{137}Cs observed among children in this area are explained by the source of their food, especially by the consumption of contaminated milk produced privately.

We stratified children from rural areas of Belarus (caesium [^{137}Cs] contamination >5 Ci/km^2) by their ^{137}Cs loads into three distinct groups (group 1, <5 Bq/kg body weight [BW]; group 2, 38.4 ± 2.4 Bq/kg BW; group 3, 122 ± 18.5 Bq/kg BW). We determined the relationship between the ^{137}Cs load and the children's main source of food and recorded their cardiovascular symptoms. Cardiovascular symptoms, ECG alterations, and arterial hypertension were significantly more frequent in children with high ^{137}Cs burden than in children with very low ^{137}Cs burden.

Children with moderate and high ^{137}Cs loads (groups 2 and 3) received apple pectin, a food additive, for 16 days. Apple pectin significantly decreased ^{137}Cs loads in these groups (39% and 28%, respectively). ECG alterations improved, while cardiovascular symptoms and hypertension did not change in any group.

Key words: Chernobyl nuclear power accident; caesium contamination; cardiovascular symptoms; hypertension; apple pectin

Introduction

Seventeen years after the nuclear power accident at Chernobyl, 60% to 80% of the artificial irradiation of the population of Southern Belarus is caused by incorporation of long-lived radioisotopes. It is known that the varying ^{137}Cs loads observed among children in this area are explained by the source of their food, especially by the consumption of contaminated milk produced privately.

^{137}Cs mainly concentrates in endocrine glands, pancreas, thymus, and heart. In these organs, levels 10 to 100 times higher than those in other organs are found in children [1].

In addition to gamma rays, ^{137}Cs also emits beta rays that are considerably more cytotoxic than gamma rays, but they reach cells only below a millimetre range. Spectrometric assessment of gamma rays liberated by ^{137}Cs allows to determine the average total whole-body load.

In contaminated areas of Chernobyl, children suffer from more chronic and severe diseases compared to those living in less contaminated areas. Recurrent respiratory and gastrointestinal infections as well as endocrine disorders and cataracts are common. Other frequent findings include increased fatigue or apathy and chest pain associated with cardiovascular symptoms, such as unstable blood pressure or arterial hypertension. Abnormal electrocardiograms (ECGs) showing sinus arrhythmia, repolarisation, and conduction abnormalities appear to be most frequent among children with high ^{137}Cs loads [2].

Autopsies performed in the Gomel area showed that heart disease and cases of sudden death were often associated with high levels of ^{137}Cs in the myocardium. Histological studies revealed degenerative alterations and focal necrosis of cardiomyocytes, with interstitial oedema but little inflammatory or vascular changes present in most cases. Similar cardiomyopathy was experimentally induced in rats exposed to ^{137}Cs [3, 4].

There is considerable interest in the search of an agent capable of lowering the radioactive burden after accidental exposure to radioactive

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isotopes, eg, ^{137}Cs. The American Food and Drug Administration (FDA) has been actively encouraging the pharmaceutical industry to develop ferrocyanide (Prussian blue), a drug that binds ^{137}Cs in the gut, thus enabling excretion of the complex in the faeces [5, 6]. In the Chernobyl area, Prussian blue is generally mixed into cattle feed to reduce the ^{137}Cs concentration in milk.

Pectins are polysaccharides found in different fruits and roots. Apple pectin is widely used in the preparation of jelly, jam, and pastry. Pure pectin tablets are used in the treatment of heavy metal intoxication. Oral apple pectin inhibits the incorporation of both ^{137}Cs and Sr-90 in rats fed with radio-contaminated food [7]. The safety of apple-pectin preparations and their activity in heavy metal intoxication in humans were shown by Gres et al. [8]. In a double-blind, placebo-controlled trial, oral apple pectin powder, given for 23 days to children receiving radioactively clean food, lowered the ^{137}Cs burden by some 60%, while the "clean" diet alone lowered the burden by only 14% [9]. Since 1996, different apple pectin preparations have been used in the Chernobyl regions of the Ukraine and Belarus to protect children in the most contaminated areas. So far, some 70,000 children in Belarus have received up to four 1-month pectin courses per year.

School children living in areas contaminated with ^{137}Cs (5–15 Ci/km^2) receive radiologically clean food at school and have the possibility of spending a holiday at a sanatorium (the initial duration of 4 weeks has been shortened to 3 weeks 2 years ago for economical reasons). There, the children are medically supervised and receive good food and daily multivitamins.

We aimed to establish a correlation between the degree of radio-contamination and regular intake of privately produced food in 'Chernobyl' children stratified by their ^{137}Cs loads. Moreover, we studied the frequency of cardiovascular symptoms in relation to the ^{137}Cs load. Additionally, the effect of apple pectin on ^{137}Cs burden and cardiovascular symptoms was determined.

Patients and methods

Study design and patients

The study was conducted at the sanatorium Silver Spring of Svetlogorsk, where about 900 school children from radio-contaminated areas of the Gomel province were spending a 3-week holiday. Radiometrists of the Belrad Radioprotection Institute measured the children's ^{137}Cs loads using an established anthropogammametric method (Screener-3M) with electronic registration [9].

In the presence of parents and a member of the Ethics Committee, all children were informed about the trial. The children gave their oral consent and the mothers their written consent.

The children were allocated to three groups, depending on their C-137 loads measured at entry. Overall, 94 children (46 boys and 48 girls), aged 7 to 17 years, volunteered to participate. Apart from the varying ^{137}Cs levels, the groups were comparable with respect to age and gender distribution (table 1).

The 31 children of group 2 with moderate ^{137}Cs burden (average 38.4 ± 2.4 Bq/kg BW) and the 30 children of group 3 with high burden (average 122 ± 18.5 Bq/kg BW) received apple pectin powder (one spoonful of Vitapect®; approx. 5 g [containing 16% pectin], taken with water or milk during meals) twice a day for 16 days.

Assessments

^{137}Cs loads were determined at the beginning and end of the study. To explain the varying ^{137}Cs burden in individual children, their eating habits and source of food were recorded. A paediatrician examined the children at study entry and after the 16-day intake of pectin powder. The assessment was blind, ie, the paediatrician did not know the ^{137}Cs loads of the children.

At the beginning and the end of the study, ECGs were recorded. Subjective complaints were elicited and arterial blood pressure was determined after moderate exercise (ie, 10 knee-bends).

Statistical analyses

Student's t-test was used for comparisons between groups.

Table 1
Demographic data and percentage of children consuming privately produced food.

Groups (No. of children; average ^{137}Cs load at entry)	boys / girls	average age (years; boys/girls)	privately produced food N (% of total)
Group 1: low radio-contamination (n = 33; <5 Bq/kg body weight)[a]	16/17	10.8/12.5	19 (58%)[c]
Group 2: moderate radio-contamination (n = 31; 38 ± 2.4 Bq/kg body weight)[b]	17/14	12.8/12.2	22 (71%)
Group 3: high radio-contamination (n = 30; 122 ± 18.5 Bq/kg body weight)	12/18	12.7/12.7	30 (100%)

[a] All values were below the precise spectrometric detection limit (5.0 Bq/kg body weight).
[b] ^{137}Cs burden in this group was similar to that of children taking part in the first controlled study of pectin versus placebo [9].
[c] The proportion of children receiving privately produced food was statistically significantly lower in group 1 than in either groups 2 or 3 (p <0.05).

Results

Correlation between baseline ^{137}Cs load and source of food

The difference in ^{137}Cs loads between the groups appeared to be explained, at least in part, by the source of the children's food (table 1). The proportion of children receiving a privately produced diet was statistically significantly lower in group 1 than in either group 2 or group 3 ($p < 0.05$).

Effect of pectin on ^{137}Cs load

As shown in figure 1, the average reduction of ^{137}Cs loads after pectin intake for 16 days amounted to 39% in children with moderate radio-contamination (group 2), and to 28% in children with high ^{137}Cs radio-contamination (group 3). The reduction from baseline was statistically significant in both groups ($p < 0.05$).

Subjective findings

Subjective complaints reported by many children included pain in the region of the heart, headache, weakness, irritability, and nasal bleeding. As shown in table 2, such complaints were expressed by 10 children (30%) in group 1, 12 children (39%) in group 2, and 19 children (63%) in group 3. In addition, 10 children (30%) in group 3 (high radio-contamination) reported permanent fatigue and depressive mood. At the end of the stay at the sanatorium, the children had practically no subjective complaints any longer.

Cardiovascular symptoms

At baseline, abnormal heart sounds were noted in 16 children (48%) in group 1, 26 children (84%) in group 2, and 27 children (90.0%) in group 3 (table 2). The difference between group 1 and each of the other two groups was statistically significant ($p < 0.05$).

At study entry, arterial hypertension (defined as arterial blood pressure exceeding the age-relevant upper limit by 20 mm Hg) was present in 3 children (9%) in group 1, 8 children (26%) in group 2, and 15 children (50%) in group 3 (table 2). The difference between group 1 and each of the other two groups was statistically significant ($p < 0.05$). Hypotension was present in up to 10% of children, with the highest percentage noted in group 3 (figure 2).

During the observation period, the percentages of children with hypertension did not change in any group.

ECG findings

At study entry, pathological ECG findings were noted in 17 children (52%) in group 1, 26 children (84%) in group 2, and 29 children (93%) in group 3 (table 2). The difference in percentages of pathological ECG findings between group 1 and the other two groups was statistically significant ($p < 0.05$).

Nine children (group 1, n = 6; group 2, n = 2; group 3, n = 1) refused the second ECG without giving any reason. The percentage of altered ECGs in group 1 (no pectin given) remained unchanged after the study (52% vs. 51%), although the children received quality food and vitamins. In groups 2 and 3, ECG alterations improved only slightly (72% vs. 87% in group 2; 79% vs. 93% in group 3; see figure 3). However, the pooled pectin groups (groups 2 and 3 combined) exhibited a statistically significant reduction ($p < 0.05$).

Tolerability

The pectin powder was well tolerated by all children.

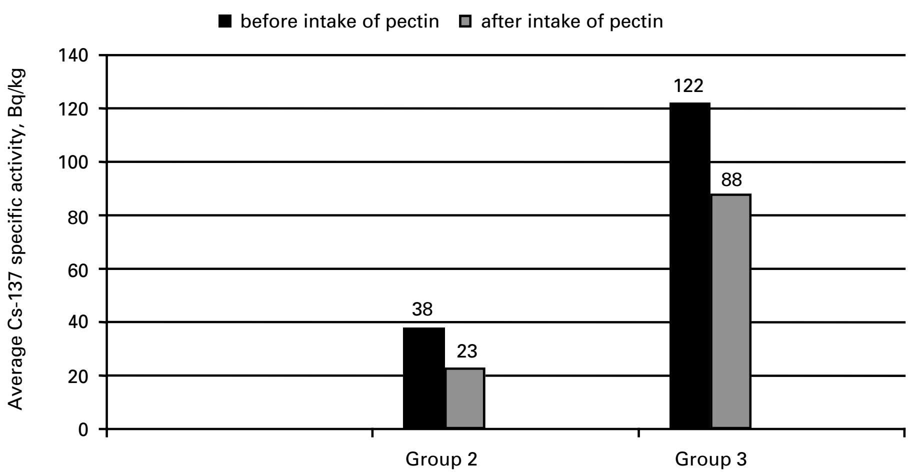

Figure 1

^{137}Cs loads before and after pectin intake for 16 days are shown for groups 2 and 3 (group 1 did not receive any pectin, the ^{137}Cs loads remained <5.0 Bq/kg BW). Group 2, moderate radio-contamination: ^{137}Cs loads decreased from 38 Bq/kg BW to 23 Bq/kg BW (39% reduction; $p < 0.05$). Group 3, high radio-contamination: ^{137}Cs loads decreased from 122 Bq/kg BW to 88 Bq/kg BW (28% reduction; $p < 0.05$).

Table 2

Clinical findings at study entry.

Groups (N)	subjective complaints N (%)	arterial hypertension N (%)	abnormal heart sounds N (%)	altered ECGs N (%)
Group 1 (n = 33)	10 (30%)	3 (9%)[a]	16 (48%)a	17 (52%)[a]
Group 2 (n = 31)	12 (39%)	8 (26%)	26 (84%)	26 (84%)
Group 3 (n = 30)	19 (63%)	15 (50%)	27 (90%)	28 (93%)

[a] The difference between group 1 and group 2 or group 3 was statistically significant ($p < 0.05$).

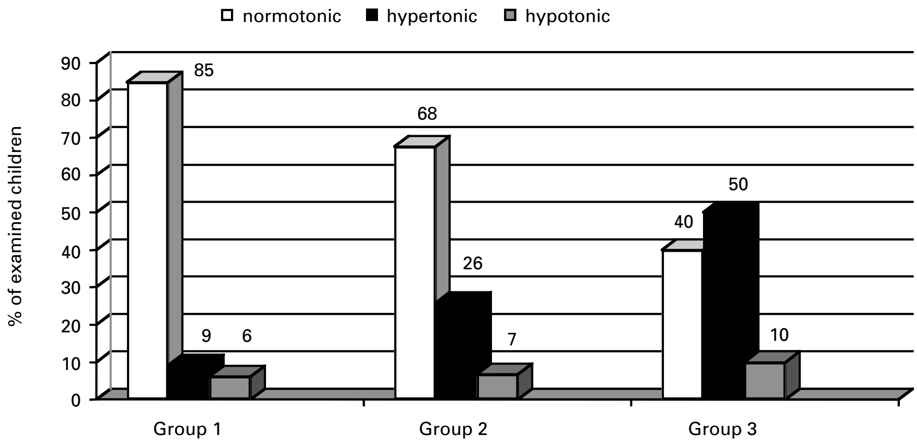

Figure 2

The percentages of normotensive, hypertensive, and hypotensive children at study entry are shown. Group 1: low radio-contamination (n = 33; <5 Bq/kg BW); group 2: moderate radio-contamination (n = 31; 38 ± 2.4 Bq/kg BW); group 3: high radio-contamination (n = 30; 122 ± 18.5 Bq/kg BW).

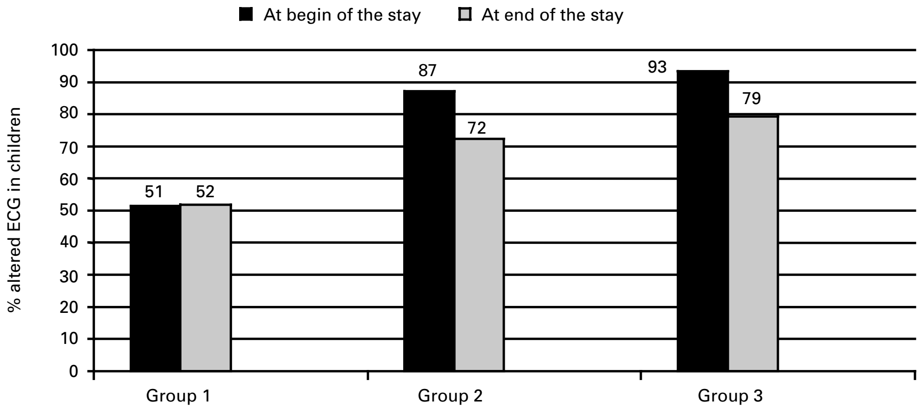

Figure 3

Percentages of altered ECG patterns at study entry and study end are shown for groups 1, 2, and 3. Group 1 did not receive any pectin. Changes in pathological ECG patterns in group 2 and group 3 were only moderate and did not reach statistical significance. The percentages calculated for the pooled pectin groups (groups 2 and 3 combined) showed a statistically significant improvement from baseline after the 16-day pectin course ($p < 0.05$).

Discussion

This preliminary study showed a clear correlation between baseline ^{137}Cs burden and the feeding habits of the children from the Gomel area. All highly radio-contaminated children (group 3) were fed on privately produced food probably containing high levels of ^{137}Cs. It is well known that privately grown vegetables and milk produced at home represent a major risk of radioactive contamination. The use of ashes as fertilisers from highly contaminated wood collected in the forests leads to an increase in the ^{137}Cs burden in the alimentary chain, ashes contributing also to an external irradiation in the kitchen, close to the fireplace. Mushrooms and wild berries consumed at home are another important source of radioactive contamination, but this factor is difficult to quantify based solely on questioning of the children and their families.

In addition, there was a correlation between baseline ^{137}Cs loads and pathological cardiovascular findings, with the largest number of cardiovascular symptoms and ECG changes noted in group 3 (high radio-contamination). Pectin administration for 16 days had little effect on cardiovascular variables but resulted in some improvement of pathological ECG patterns. The effect on ECG changes was statistically significant only if the two groups receiving pectin were pooled.

At baseline, a relatively large proportion of children had abnormal heart sounds. In children with a higher ^{137}Cs burden (groups 2 and 3), the frequency of abnormal heart sounds was much higher than in the children with low radio-contamination. The reason for this difference remains unclear.

Pectin intake reduced the ^{137}Cs burden by 39% and 28% in the groups with moderate and high radio-contamination; however, the absolute reduction was higher in group 3. The treatment duration of 16 days appears to be too short to lower the ^{137}Cs burden more effectively, especially in children with high ^{137}Cs contamination at baseline.

To determine if prolonged pectin administration significantly improves the clinical status of children, we are planning an extended prospective, placebo-controlled, double-blind study with pectin in a larger population of children with varying levels of radio-contamination.

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Radiation protection – Arguments against the easing of rules recommended by the ICRP (International Commission on Radiation Protection)

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Abstract

In September of 2005, the IRPA (International Radiation Protection Association) will present, discuss and adopt its draft in Geneva and as a result will present guidelines for the national radiation protection commissions. The changes proposed in this Draft 2005 are unacceptable in view of great scientific uncertainties in radiation biology and must be rejected. The Swiss Confederation has modern and well thought-out radiation protection laws and a sound radiation protection ordinance. It is in the best interests of our country to adhere to its own code of practice (see letter to the editor SaeZ 3/2005). There are ample reasons to uphold the current, conservative Swiss radiation protection regulations. These reasons will be presented in the following.

Based on leukemia cases in children, epidemiological data is presented and pathogenic mechanisms relating to the formation of malignant tumors are discussed. The main focus will be ion the chapter of ionizing radiation.

Which mechanisms lead to the aberration of cell proliferation and the formation of malignant tumors? Which new findings and research fields are evolving in this context? The concrete example of the leukemia epidemic in Sellafield is used to list a number of different explanation mechanisms, such as the hypothesis of direct external radiation and radioisotope absorption, the theory of preconceptual radiation of the fathers of children affected by leukemia and the theory of the interference of urban population groups in rural population groups. We will point out the multi-factorial tumor genesis and the fact that operation of nuclear power stations may in fact have an effect on leukemia genesis.

Sellafield – The so-called reprocessing of nuclear waste – Effects on public health

In 1983, the Yorkshire Television Company aired a program prepared by Butler. The journalist had initially investigated health problems of workers at the reprocessing plant at Sellafield. When interviewing the workers, he became aware of an increased number of leukemia cases in a nearby village named Seascale. 5 leukemia cases had occurred in children under the age of 10, thus 10 times the normal risk.

Startled by this report, the British government decided to have the epidemic investigated and commissioned an advisory group chaired by chairman Sir Douglas Black to perform a scientific study on the increase in childhood leukemia occurrences in the Sellafield area.
The increased incident rate was indeed confirmed by the "Independent Advisory Group" of Sir Douglas Black, the assumption however that the cancer cases were caused by emissions from the nuclear waste reprocessing plant could not be validated. Thus the first hypothesis of a direct effect of reprocessing and power production at the Sellafield plant had to be eliminated.

The recommendations of the "Report of the Independent Advisory Group" were adopted by the British government and COMARE (Committee on Medical Aspects of Radiation in the Environment) was founded. Martin Gardner had been one of the members of the "Independent Advisory Group" of Sir Douglas Black and as a member of COMARE, Martin Gardner and his staff studied the incidence of leukemia in the Sellafield area.
In order to prepare epidemiological evidence, Gardner performed a control case study which indicated that the illness of the children could be traced to the occupation of the fathers at the nuclear plant at Sellafield.

British Nuclear Fuel (BNFL) submitted the complete radiation dose records for workers at their plant and in his control case study Martin Gardner found a clear correlation between high workplace radiation contamination and leukemia and non-Hodgkin lymphoma incidents (LNHL) in children of contaminated fathers. (Table 1). Subsequently, the findings of Gardner were criticized; an increased number of leukemia incidents in other nuclear plants where prospective fathers were exposed to comparable levels of radiation, could not be validated. Later, another hypothesis was suggested by Kinlen. Kinlen had found local clusters of childhood leukemia in several studies. These clusters always appeared after large urbane population groups had permeated rural areas.

In World War II, when the city of London was heavily bombarded, the inhabitants had to flee the city and were transferred to rural areas. Oil industry workers from the city, temporarily moved to rural areas in order to work in the north of Scotland. When the Sellafield plant was built and started operation, more and more urbanites moved to the Sellafield area. The Kinlen Hypothesis is based on the assumption that urbanites had been in contact with more and different viruses than the rural population and that these newcomers from cities brought viral infections to the countryside where leukemia in children was triggered as a rare symptom of a viral infection[8].

But even this hypothesis does not explain the increase in childhood leukemia incidences in Sellafield, but only explains half the cases[9]. In addition, no virus was identified which could be made accountable for the incidence of leukemia.

Leukemia and non-Hodgkin lymphoma incidence in children and young adults under the age of 25 in Westcumbria (Gardner et al 1990)		
Cumulative external dose (mSv) father was exposed to	Local control	Area control
1-49	1,06	0,53
50-99	1,16	0,95
100-	6,42	8,3

Table 1: Correlation between incidences of childhood leukemia/non-Hodgkin lymphoma and radiation doses to which fathers are exposed before conception of these children compared with one local and one regional control group.

At the “Childhood Leukemia Conference” in London, Bryn Bridges, the current president of COMARE, on September 7, 2004 showed a slide and asked the following question: “Maybe Gardner was right in Seascale?”, even though COMARE had rejected Gardner’s hypothesis. But the same day, Bridges also quoted Paul Anderson to illustrate the complexity of the Sellafield story, with something each scientist should always take to heart: “I have never encountered any problem however complicated which, when looked at in the proper way, did not become still more complicated”.

In conclusion: there are many open questions regarding the childhood leukemia cases in Sellafield, nevertheless, on September 7 in London, Bryn Bridges, COMARE’s president, put forward the questions: “Maybe Gardner was right in Seascale?” And: the Sellafield story continues.

Have we reached the limits of the classical epidemiological research?

The classical epidemiological research has not been able to provide us with definitive findings regarding the increase of childhood leukemia incidences in Sellafield. The hypotheses on which the research was based or which were developed during the studies could neither be validated nor definitely rejected in their entirety. It is possible that a refinement of the epidemiological research may be helpful. To date, research was based on the assumption that a quantitative difference of individual responses did indeed exist, but that these responses could not be classified in detail. Using gene technological methods, a clearly defined genetic predisposition could be determined to define sub populations reacting much more sensitively to radiation. For this reason, molecular epidemiology is set to gain significance.

Genome instability and bystander effect

In the past 10 years, a paradigm change in the impairment mechanisms of the cell nucleus has been in the offing. In classical models it was always assumed that a cell hit by an energy incident (radiation hit) had not properly repaired the damage (e.g. a gene mutation) and transferred it to all daughter cells formed by the division of this cell. Recently it has been noted that the cell being exposed to external radiation may be fully repaired, but that after exposition to radiation, and incidentally to other toxic substances as well, effects in descendants of the exposed cells, can be studied many cell divisions later to an extent which would have been expected only shortly after exposition (fig. 1). Many cell generations later, chromosome abnormalities, micronuclei and defective or modified genes and potentially false gene expressions can be found. This genome instability may possibly also be transferred to other unaffected cells of a tissue by the so-called bystander effect, as a result also leading to genome instability in cells many cell divisions later not originating from the affected stem cell.

Genome instability has not yet been fully figured out in detail, and the importance of the bystander effect (feedback about damage to other cells) is not yet clear. The bystander effect may as well point in a positive direction, by warning other cells to be vigilant and signals are received which may very well stimulate and boost repair mechanisms. Genome instability leads to malignant tumors, among others.

To date, genome instability has been described in labs mostly in connection with alpha radiation (high LET radiation). Recently, studies have been published dealing with gamma radiation (low LET radiation). The current scientific discussion evolves around the questions if low gamma radiation doses may lead to genome instability and triggering of the bystander effect.

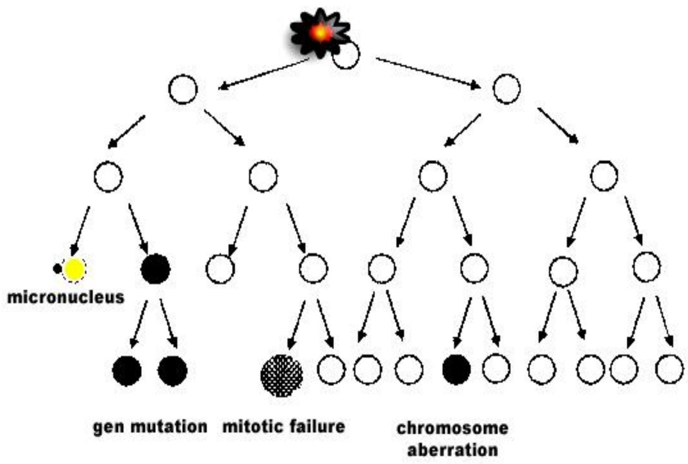

Figure 1: Example for radiation damage to a stem cell. Above, the incident (designated as hit) on a stem cell. This stem cell is then repaired, divides and damage only occur in descendants.

If this were the case, the risks of thin ionized radiation may have to be described in a new way. It is worth mentioning that genome instability may not only be transferred intraindividually to other cells during cell division, but may also be transferred to later generations via the germ line.

In a 2001/2002 publication, the German Radiation Protection Commission SSK advocated a dramatic increase in research activities in the areas of genome instability and bystander effect, in particular the study of the importance of genetic predisposition and genome instability for individual radiation sensitivity.

The risks of ionized radiation – Even medicine has (long since) lost its innocence

Risk assessment of ionized radiation is based on comparison of populations exposed and not exposed to radiation with excess mortality rates in cancer cases. The most important base is the life span study of Hiroshima and Nagasaki survivors. However, there are also basic findings in medicine. Therapeutic and diagnostic activities of doctors considered irresponsible today have also contributed to risk description.

In summary, these are:

- ray treatment of Spondylitis ankylopoetica
- ray treatment of Tinea capitis
- fluoroscopy in TBC/pneumothorax treatment (mammacarcinoma)
- mastitis ray treatment (mamacarcinoma)
- Thymus ray treatment
- Thorostrast in liver diagnosis

In addition, there is data gathered from studying occupational hazards in the nuclear sector:

- uranium miners
- liquidators (Chernobyl clean-up)
- workers in nuclear power plants and in the bomb building sector

Lately, we as doctors are working on establishing another database, to put it cynically. According to David J. Brenner from Columbia University, New York, the introduction of multislice spiral CTs in pediatrics has led to an explosion of pediatric CT examinations in the US and the UK. The doses newborns and children are exposed to are comparable to those of Hiroshima and Nagasaki. Brenner estimates that in the US alone, CT examinations may be the cause for 2500 malignant tumors in children per year.

Mutations in the minisatellite genome detected after Chernobyl, but not after Hiroshima and Nagasaki – the consequence of radiation for future generations

On April 25, 1996 a group working with Dubrova published a study on the increased rate of mutations in the mini - satellite genome. Children born in the Mogilev region between February and September of 1994 and their fathers and mothers (both parents must have lived in the area for all their life) were DNA fingerprinted. They were compared with a collective of Caucasian children of the same age and gender from non-contaminated regions in England. In correlation with the level of ground contamination in cesium, Dubrova found an increase of the mutation rate in the minisatellite genome which was almost twice the average. The same methods were used to examine the children of Hiroshima and Nagasaki survivors and no increased mutation rates could be established.

The Chernobyl accident seems to have had a totally different biological importance compared to the American bombardment of Hiroshima and Nagasaki with atomic bombs. This study points in the direction of the findings of Martin Gardner who had found epidemiological evidence for germ line genesis in leukemia formation in the children of Sellafield, but it also confirms the hypothesis proposed by Louise Parker, i.e. that more stillbirths occur when the germ line is damaged by ionized radiation in cases where fathers had been exposed before conception.

In 2001, Weinberg and his group published another study in the Proceedings of the Royal Society in London. 700 liquidators from the former Soviet Union had emigrated to Israel. Liquidators are people who were employed in clean-up operations after the Chernobyl disaster. Mostly young men had been conscripted for these operations, but also Ukrainian families. In all selected families, the fathers were liquidators with the exception of one couple, where both partners had worked as liquidators. One of the groups studied were Israeli immigrants, the other Ukrainian citizen. One condition to be accepted for the study was that one child of the family had to be conceived before the clean-up, another child after the clean-up. 41 children born after cleanup and 22 children born before the cleanup as well as their parents were examined. A control population of 14 families with 28 children from a region not contaminated by radiation was examined as well. The children of liquidators, i.e. fathers exposed to radiation, conceived after the accident showed a 7-times higher mutation rate in the minisatellite genome than the children conceived before the accident. Weinberg had also pointed out that this increase in mutation rates had not been found by Satoh and Kodaira in children of the atomic bomb survivors in Japan. Dubrova however criticizes the Weinberg studies, since the polymerase chain reaction (PCR), the random amplified polymorphic DNA-PCR (RAPD-PCR) might produce random results. This data should therefore be validated by representation of mutations.

The objection that mutations in the minisatellite genome are mutations without harmful consequences , since the minisatellite genome does not have coded sections, is rejected by geneticists in the group of Dubrova, since there are clear indications that the radiation of male germ cells can lead to transgenerational genome instability, most probably caused by a hereditary dysfunction of the DNA damage repair mechanisms and may therefore lead to cancer, behavioral disorders, fertility disorders, increased mortality and somatic damage to the cells.

In summation, we have to state that there are a multitude of open questions, which by far have not yet been answered. As long as we do not know more, we have to be extremely cautious and the idea of easing the radiation protection regulations at this point in time is less than welcome. And this is exactly what the IRPA will demand in their Draft 2005 meeting in Geneva in September.

There is an old oriental proverb: “When the dust settles, you will see whether you ride a horse or an ass.”

The dust has not yet settled!

Strahlenschutz – Argumente gegen die von der ICRP (Internationale Kommission für Strahlenschutz) vorgesehenen Lockerungen der Regeln

*M. Walter**

Die ICRP (International Commission on Radiological Protection) wird im September 2005 in Genf ihren Draft 2005 vorlegen, diskutieren und dann verabschieden. Sie gibt damit die Richtlinien für die nationalen Strahlenschutzgremien vor. Die im Draft 2005 [1] vorgeschlagenen Lockerungen sind angesichts grosser wissenschaftlicher Unsicherheiten in der Strahlenbiologie nicht zu verantworten und müssen zurückgewiesen werden. Die Schweizerische Eidgenossenschaft hat ein modernes und durchdachtes Strahlenschutzgesetz und eine vernünftige Strahlenschutzverordnung. Unser Land hat jegliches Interesse, an seinem Regelwerk festzuhalten [2]. Es gibt Gründe zum Erhalt des aktuellen, konservativen Schweizerischen Strahlenschutzes. Diese Gründe sollen dargelegt werden.

Anhand der kindlichen Leukämie werden epidemiologische Daten präsentiert und pathogenetische Mechanismen der Entstehung von malignen Tumoren besprochen. Der Schwerpunkt wird auf das Kapitel ionisierende Strahlung gelegt.

Welche Mechanismen führen zur Entgleisung der Zellproliferation in Richtung maligner Tumoren? Welche neuen Erkenntnisse und Forschungsgebiete zeichnen sich dabei ab? Am Beispiel der Leukämieepidemie in Sellafield werden verschiedene Erklärungsmechanismen aufgezählt, wie die Hypothese der direkten Bestrahlung von aussen und der Radioisotopenaufnahme, die Theorie der präkonzeptionellen Bestrahlung des Vaters des leukämiekranken Kindes und die Theorie der urbanen Bevölkerungseinmischung in rurale Bevölkerungsgruppen. Es wird auf die multifaktorielle Tumorgenese hingewiesen, und es wird aufgezeigt, dass der Betrieb von Atomanlagen tatsächlich einen Effekt auf die Leukämiegenese haben könnte.

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Sellafield – die sogenannte Wiederaufbereitung von Atommüll – Auswirkungen auf die Gesundheit der Bevölkerung

1983 wurde von der Yorkshire Television Company ein Beitrag von Cutler ausgestrahlt. Der Journalist hatte eigentlich in der Wiederaufbereitungsanlage von Sellafield nach gesundheitlichen Störungen bei den dort angestellten Arbeitern gesucht. Bei der Befragung dieser Arbeiter war er auf eine Häufung von Leukämien im angrenzenden Seascale, einem kleinen Dorf, gestossen. Fünf Fälle von Leukämie waren bei <10jährigen aufgetreten, was ein 10fach erhöhtes Risiko bedeutete.

Aufgeschreckt durch diesen Bericht hat die britische Regierung die Epidemie untersuchen lassen und dafür eine Gruppe unter der Führung des Chairman Sir Douglas Black beauftragt, eine wissenschaftliche Studie über die Inzidenzsteigerung kindlicher Leukämie in Sellafield zu verfassen [3]. Die erhöhte Inzidenz konnte von der «Independent Advisory Group» um Sir Douglas Black bestätigt werden, hingegen konnte die Vermutung, dass die Krebsfälle aufgrund der Emissionen aus der Wiederaufbereitungsanlage von Atommüll aufgetreten waren, nicht bestätigt werden. Somit wurde die erste Hypothese, nämlich diejenige einer direkten Auswirkung der Wiederaufbereitung und der Stromproduktion in der Anlage von Sellafield, ausgeschlossen.

Die Empfehlung des «Report of the Independent Advisory Group» wurde von der englischen Regierung aufgenommen, und es wurde deshalb die COMARE (Committee on Medical Aspects of Radiation in the Environment) [4] gegründet. Martin Gardner war eines der Mitglieder der «Independent Advisory Group» um Sir Douglas Black gewesen, und Martin Gardner untersuchte als Mitglied der COMARE mit seinen Mitarbeitern die Leukämiegenese in der Umgebung von Sellafield. Zur Erarbeitung der epidemiologischen Indizien führte Gardner eine Fallkontrollstudie durch, die darauf hinwies, dass die Erkrankung der Kinder auf die Beschäftigung der Väter in der Atomanlage von Sellafield zurückzuführen sein könnte [5, 6]. British Nuclear Fuel (BNFL) stellte sämtliche Dosisrecords der in ihrer Anlage Arbeitenden zur Verfügung, und Martin Gardner fand in einer Fallkontrollstudie eine eindeutige Korrelation zwischen hohen Arbeitsplatzbelastungen mit Radioaktivität und der Leukämie- und Non-Hodgkin-Lymphom-Inzidenz (LNHL) bei Kindern dieser belasteten Väter (Tab. 1).

Diese Arbeit von Gardner wurde in der Folge kritisiert; bei anderen Atomanlagen mit ähnlichen Dosen auf die zeugenden Väter konnte der Befund erhöhte Leukämieinzidenz der ge-

Tabelle 1
Abhängigkeit der Inzidenz kindlicher Leukämie und Non-Hodgkin-Lymphom von der Dosis auf die Väter vor der Zeugung der betroffenen Kinder mit je einer lokalen und einer regionalen Kontrollgruppe. Leukämie- und Non-Hodgkin-Lymphom-Inzidenz bei unter 25jährigen Kindern und Jugendlichen in Westkumbrien [5, 6].

Dosis (mSv) auf den Vater	Lokale Kontrollen	Gebietskontrollen
1–49	1,06	0,53
50–99	1,16	0,95
100–	6,42	8,30

zeugten Kinder nicht gefunden werden [7]. Später wurde eine weitere Hypothese durch Kinlen vorgeschlagen. Dieser hatte in mehreren Studien lokale Cluster von kindlicher Leukämie gesehen. Diese Cluster entstanden immer dann, wenn hohe Einmischungen urbaner Bevölkerungsteile in rurale Gegenden stattgefunden hatten.

Im Zweiten Weltkrieg, als die Stadt London bombardiert wurde, musste die Bevölkerung aus der Stadt fliehen und wurde in ländlichen Gegenden untergebracht. Ölarbeiter aus städtischen Gebieten nahmen vorübergehend Wohnsitz in ländlichen Gebieten, um im Norden Schottlands zu arbeiten. Der Bau der Anlage von Sellafield und deren Betrieb brachte immer wieder urbane Bevölkerungseinmischungen in die Gegend von Sellafield. Die Kinlen-Hypothese geht davon aus, dass urbane Bevölkerungsgruppen mit mehr und anderen Viren als rurale Bevölkerungsgruppen in Kontakt gewesen waren, dass diese Gruppen aus den Städten virale Infektionen aufs Land brachten, wo dann als seltenes Symptom einer viralen Erkrankung eine Leukämie bei Kindern ausgelöst wurde [8].

Auch diese Hypothese reicht nicht zur Erklärung der Häufung der kindlichen Leukämie in Sellafield, sondern erklärt nur etwa die Hälfte der Fälle [9]. Zudem ist kein Virus identifiziert, das für die Leukämiegenese verantwortlich gemacht werden kann.

Bryn Bridges, der derzeitige Präsident von COMARE, zeigte am 7. September 2004 an der «Childhood Leukaemia Conference» in London ein Diapositiv, in dem er fragte: «Maybe Gardner was right in Seascale?», obschon COMARE, deren Präsident Bridges ist, Gardners Hypothese verworfen hatte. Bridges zitierte am gleichen Tag aber auch Paul Anderson zur Illustration der Komplexität der Sellafieldstory, was für Wissenschaftler immer wieder zu beherzigen sein sollte: «I have never encountered any problem however complicated which, when looked at in the proper way, did not become still more complicated.»

Zusammenfassend: Viele Fragen zu den kindlichen Leukämien um Sellafield sind offen, die klassische epidemiologische Forschung gibt uns keine definitiven und valablen Antworten. Aber: «Maybe Gardner was right in Seascale?». Und: Die Sellafieldstory geht weiter.

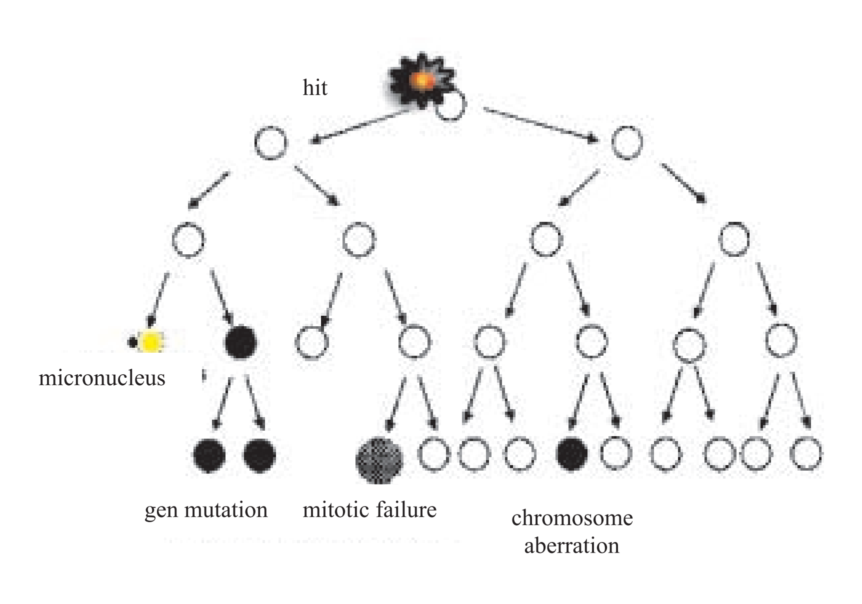
Grenzen der klassischen epidemiologischen Forschung erreicht?

Die klassische epidemiologische Forschung hat im Falle von Sellafield keine definitive Aussage zur Häufung der kindlichen Leukämie machen können. Die der Forschung zugrundegelegten oder von ihr erarbeiteten Hypothesen konnten im einzelnen weder bewiesen noch definitiv verworfen werden. Möglicherweise hilft eine Verfeinerung der epidemiologischen Forschung hier weiter. Bisher ging man davon aus, dass zwar eine quantitative Unterschiedlichkeit der individuellen Empfindlichkeit vorhanden ist, dass diese aber nicht genau definiert werden könne. Neu könnte eine definierbare genetische Prädisposition mittels gentechnologischer Methoden gezeigt und es könnten so Subpopulationen in der Bevölkerung definiert werden, die empfindlicher reagieren auf Strahlung. Es dürfte deshalb die Molekulare Epidemiologie an Bedeutung gewinnen.

Genominstabilität und Bystandereffekt

In den letzten zehn Jahren bahnte sich ein Paradigmenwechsel des Schädigungsmechanismus des Zellkerns an. Man hatte in den klassischen Modellen immer angenommen, eine Zelle, die von einem Energieereignis (Strahlentreffer) getroffen worden sei, habe den Schaden (z.B. eine Genmutation) nicht richtig repariert und ihn auf sämtliche Tochterzellen, die aus Teilung dieser Zelle hervorgegangen waren, übertragen. Neu ist aufgefallen, dass die getroffene Zelle voll repariert sein kann, dass aber nach der Exposition gegenüber Strahlung, wie übrigens auch gegenüber anderen Noxen, in den Nachkommen exponierter Zellen, viele Zellteilungen später, Effekte beobachtet werden, die man in diesem Ausmass nur kurz nach der Exposition erwartet hätte (Abb. 1). So finden sich viele Zellgenerationen später Chromosomenabnormitäten, Mikronuklei und defekte oder veränderte Gene und eventuell falsche Genexpressionen. Diese Genominstabilität kann möglicherweise auch an nicht betroffene andere Zellen in einem Gewebe über den sogenannten Bystandereffekt signalisiert werden und so auch in Zellen, die nicht von der getroffenen Stammzelle abstammen, unter anderem zur genomischen Instabilität führen.

Abbildung 1
Beispiel eines Strahlenschadens an einer Stammzelle. Oben ist das Ereignis (als «hit» bezeichnet) an einer Stammzelle beschrieben. Diese wird repariert, teilt sich und erst in ihrer Nachkommenschaft treten dann Schäden auf.



Die Genominstabilität ist noch nicht bis zum letzten Detail verstanden, ebenso wie die Bedeutung des Bystandereffektes (Meldung von Schäden an andere Zellen) in ihrer Bedeutung unklar ist. Der Bystandereffekt könnte nämlich ebensogut in eine positive Richtung weisen, indem dieser Bystandereffekt andere Zellen zur Achtsamkeit mahnt und dort Signale empfangen werden, die zum Beispiel Reparaturmechanismen anregen und verstärken könnten. Genominstabilität führt unter anderem zu Malignomen.

Bisher ist die genomische Instabilität im Labor vor allem bei Alphastrahlung (High-LET-Strahlung) beschrieben worden. Neuerdings werden aber auch Arbeiten im Bereiche der Gammastrahlung (Low-LET-Strahlung) publiziert [10]. Die aktuelle wissenschaftliche Diskussion geht nun darum, ob kleine Strahlendosen im Bereiche der Gammastrahlung zu genomischer Instabilität und zur Auslösung des Bystandereffektes führen können.

Sollte dies zutreffen, müsste eventuell das Risiko dünn ionisierender Strahlung neu beschrieben werden. Erwähnenswert ist, dass Genominstabilität nicht nur intraindividuell im Rahmen der Zellteilung an weitere Zellen weitergegeben werden kann, sondern dass Genominstabilität auch auf weitere Generationen über die Keimbahn übergehen kann.

Die deutsche Strahlenschutzkommission SSK hat in einer Publikation von 2001/2002 gefordert, dass Genominstabilität und Bystandereffekt mit vermehrtem Aufwand erforscht werden müssten, unter anderem auch zur Untersuchung der Bedeutung der genetischen Prädisposition und der genomischen Instabilität für die individuelle Strahlenempfindlichkeit.

Das Risiko ionisierender Strahlung – auch die Medizin hat ihre Unschuld (schon längst) verloren

Die Abschätzung des Risikos ionisierender Strahlung wird aus Vergleichen bestrahlter und nicht bestrahlter Populationen mit der Übersterblichkeit an Krebs hergeleitet. Die wichtigste Basis ist die Lifespanstudy an den Überlebenden von Hiroshima und Nagasaki. Es gibt aber auch Grundlagen aus der Medizin. Heute für unverantwortlich zu bezeichnende Tätigkeiten therapeutischer und diagnostischer Tätigkeiten von uns Ärzten haben ihren Beitrag zur Risikobeschreibung geliefert.

Summarisch zusammengefasst sind dies:
- Bestrahlung der ankylosierenden Spondylitis;
- Bestrahlung der Tinea capitis;
- Durchleuchtung wegen TBC/Pneubehandlung (Mammakarzinom);
- Mastitisbestrahlung (Mammakarzinom);
- Thymusbestrahlung;
- Thorotrast in der Leberdiagnostik.

Dazu kommen Daten aus der Beschäftigung in der Atomtechnologie:
- Uraniumminer;
- Liquidatoren (Tschernobylaufräumer);
- AKW-Arbeiter und Bombenbauer.

Neuerdings sind wir Mediziner daran, eine weitere Datenbasis zu liefern, um es etwas zynisch auszudrücken. Laut David J. Brenner von der Columbia University, New York, hat die Einführung des Multislice-Spiral-CTs in der Pädiatrie zu einer eigentlichen Explosion der pädiatrischen CT-Untersuchungen in den USA und in UK geführt. Die Dosen auf Säuglinge und Kleinkinder sind dabei im Bereiche der Dosen auf die Hiroshima- und Nagasaki-Überlebenden. Brenner schätzt, dass allein in den Vereinigten Staaten pro Jahr 2500 Malignome mit CT-Untersuchungen an Kindern erzeugt werden dürften [11].

Mutationen am Minisatellitengenom nach Tschernobyl, aber nicht nach Hiroshima und Nagasaki – die Folgen der Bestrahlung für kommende Generationen

Am 25. April 1996 publizierte eine Gruppe um Dubrova eine Arbeit über eine erhöhte Rate von Mutationen im Minisatellitengenom. Kinder, die vom Februar bis September 1994 in der Mogilev-Region geboren wurden, und deren Väter und Mütter (beide Eltern mussten zeitlebens in Mogilev gelebt haben) wurden mittels DNA-Fingerprints untersucht. Sie wurden verglichen mit einem Kollektiv von geschlechts- und altersgematchten Kindern kaukasischer Rasse aus nicht kontaminierten Gebieten in England [12]. Korreliert mit der Höhe der Bodenkontamination mit ^{137}Cäsium fand Dubrova eine im Durchschnitt zweifache Erhöhung der Mutationsrate im Minisatellitengenom. Mit gleichen Methoden wurden Kinder von Atombombenüberlebenden aus Hiroshima und Nagaski untersucht und es wurden dort keine erhöhten Mutationsraten festgestellt [13].

Der Tschernobylunfall scheint biologisch eine völlig andere Bedeutung zu haben als die Bombardierung von Hiroshima und Nagasaki 1945 in Japan mit amerikanischen Atombomben. Diese Arbeit weist in die Richtung der von Martin Gardner epidemiologisch erhobenen Indizien der Keimbahngenese zur Leukämieentstehung bei den Kindern in Sellafield, aber bestätigt auch die Hypothese von Louise Parker [14], dass Totgeburten vermehrt vorkommen wegen der Schädigung der Keimbahn durch ionisierende Strahlung, dies, wenn die zeugenden Väter exponiert worden waren.

Eine weitere Studie wurde in den Proceedings der Royal Society in London von Weinberg und seiner Gruppe im Jahre 2001 publiziert [15]. 700 Liquidatoren aus der ehemaligen Sowjetunion sind nach Israel ausgewandert. Als Liquidatoren werden Menschen bezeichnet, die nach dem Super-Gau von Tschernobyl als Aufräumer dort im Einsatz waren. Meistens waren junge Männer zu den Arbeiten kommandiert worden. Dazu wurden auch Familien aus der Ukraine ausgewählt. Bei allen ausgewählten Familien waren die Väter Liquidatoren mit einer Ausnahme eines Ehepaars, wo beide Partner als Liquidatoren gearbeitet hatten. Die Familien waren einerseits israelische Immigranten, andererseits ukrainische Bürger. Bedingung für die Aufnahme in die Studie war, ein Kind vor den Aufräumarbeiten gezeugt zu haben, eines nach der Aufräumarbeit. Es wurden 41 «Nachgezeugte» und 22 «Vorgezeugte» und deren Eltern untersucht, dazu eine Kontrollpopulation von 14 Familien mit 28 Kindern aus radiologisch unverseuchtem Gebiet. Die nach dem Unfall gezeugten Kinder der Liquidatoren, also der strahlenbelasteten Väter, hatten eine über siebenfach höhere Mutationsrate im Minisatellitengenom als die vor dem Einsatz als Liquidator gezeugten Kinder. Auch Weinberg weist darauf hin, dass diese Steigerung der Mutationsrate durch Satoh und Kodaira bei Kindern von Atombombenüberlebern in Japan nicht hatte gefunden werden können [11]. Die Arbeit von Weinberg wird von Dubrova kritisiert, weil die verwendete Polymerasechainreaktion (PCR), die Random amplified polymorphic DNA-PCR (RAPD-PCR), zufällige Resultate hervorbringen könne. Diese Daten müssten also validiert werden durch Darstellen der Mutationen [16].

Vorschläge des ICRP-2005-Draft zur Lockerung der Strahlenschutzregeln

In erster Linie soll die Kollektivdosislimite [1] (dose constraint = source-related limit) aufgehoben werden. Letztere besagt, dass durch eine bestimmte Tätigkeit eine maximale Strahlendosis auf eine umschriebene Gruppe von Menschen wirksam werden darf. Am Beispiel des AKW Mühleberg dürfen das (inklusive Jahreswartung des Reaktors) 4 Personensievert (= Anzahl Beschäftigte × mittlere erhaltene Personendosis in Sievert) pro Jahr sein. Die Aufhebung der Kollektivdosislimite hätte rasch eine Ausweitung der Kollektive zur Folge und nähme damit mehr Krebsfälle und – weit schlimmer – mehr genetische Schäden für zukünftige Generationen in Kauf. Gesellschaftspolitisch ist dies nicht wünschenswert, moralisch nicht zu rechtfertigen. Statt der Kollektivdosislimite schlägt die ICRP ein «Optimierungskonzept» vor, das mit dem guten Willen der Beteiligten nach mehr oder weniger schwammigen Regeln die Dosis tief halten soll. Die Regulierungsbehörde hätte damit aber kein griffiges Instrument mehr zur Verfügung und könnte bei einem aus dem Ruder laufenden Prozess nicht mehr intervenieren.

Ferner beabsichtigt die ICRP, stärkere radioaktive Kontaminationen von Lebensmitteln als bisher zuzulassen. Dies ist ein unhaltbarer Vorschlag angesichts der bereits eingetretenen grossflächigen radioaktiven Bodenverseuchung durch die Katastrophe von Tschernobyl.

Der Einwand, dass es sich bei den Mutationen im Minisatellitengenom um Mutationen ohne gesundheitsschädigende Auswirkungen handle, weil das Minisatellitengenom keine codierenden Abschnitte aufweise, wird von einer Gruppe von Genetikern um Jurij Dubrova zurückgewiesen, da es deutliche Hinweise darauf gebe, dass die Bestrahlung von männlichen Keimzellen zur transgenerationellen Genominstabilität führen könne, wahrscheinlich durch eine vererbte Störung von Reparaturmechanismen von DNA-Schäden, die so zu Krebs, Verhaltensstörung, Fertilitätsstörung, erhöhter Sterblichkeit und somatischen Schäden an den Zellen führen könne [17].

Zusammenfassend liegen viele offene Fragen vor, die noch nicht annähernd geklärt sind. Solange wir nicht mehr wissen, ist äusserste Vorsicht angezeigt und eine Lockerung des Strahlenschutzes alles andere als wünschenswert im jetzigen Zeitpunkt. Und eine solche Lockerung wird von der ICRP an ihrer Draft-2005-Sitzung im September in Genf gefordert werden.

Ein orientalisches Sprichwort sagt: «When the dust settles you will see whether you ride a horse or an ass.» Der Staub hat sich noch nicht gesetzt!

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