Stralingsbescherming in de radiologie
Röntgenonderzoeken en zwangerschap
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Risks of X-rays examinations during pregnancy: scientific background

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Current « knowledge »

Distinguish:

Widespread views within experts

Statements from reputable committees

Corpus of scientific data and uncertainties

Irradiation in utero in early phases: current views and statements: the 100 mSv break-point

- **Pre-implantation** period: all or nothing : possible death of embryo above 0.1 Gy; if not killed the embryo develops normally; no congenital malformation

- **Early organogenesis**: no congen. malf. under 0.1 Gy ICRP 103: " there is a **true dose threshold** of around 100 mGy"
  - 100 mSv frequently presented as the "official" break-point criterion in situations like emergency planning, or post-accidental decisions

100 mGy? ICRP 90: more nuances

- **Pre-implantation** period: no congenital malformation, but exceptions mentioned (“due to genetic predispositions”)

- **Early organogenesis**:

  dose range of **50** - 250 mGy

Irradiation during the Pre-implantation period (day 0-5)

classical view: possible death of embryo above 100 mGy

Animal experiments: possible death already at 50 mGy in some studies

Irradiation during the Pre-implantation period (day 0-5)

- research on Zygote (1 cell):
  - Animal strains ***susceptible*** to spontaneous congenital malformation (Streffer): induction of congenital malformation, with apparently **no threshold**; same malformations as the spontaneous ones;
  - Animal strains ***not susceptible*** to spontaneous congenital malformation (Gu) : induction of congenital malformation **with threshold** at about 0.1 Gy

% malform.*

S. PAMPFER AND C. STREFFER (1988)

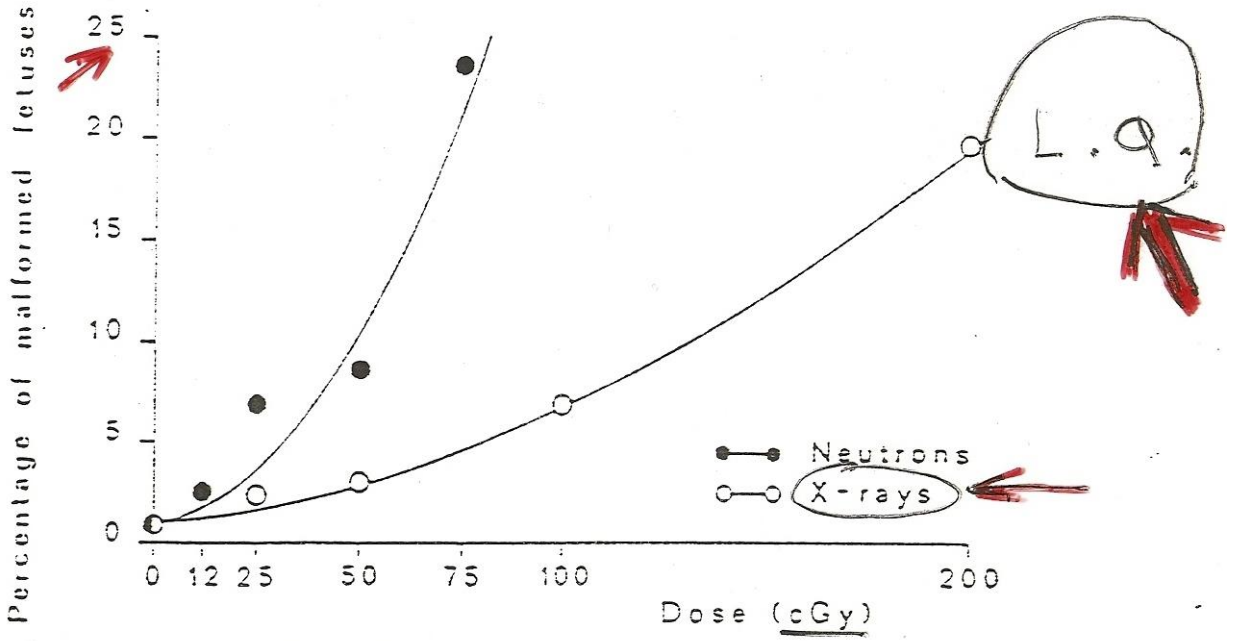


Fig. 2. Incidence of ~~externally~~ malformed fetuses at gestation day 19 as a function of the neutron or X-ray dose.

Mice (first h. preimplan. stage) : single cell stage

(cfr. stochastic effects)

Irradiation during the Pre-implantation period (day 0-5)

- research on 2-, 4-, 8-, 16 (morula)-, 32 (blastocyst) cell :
  - induction of congenital malformation *with threshold but less frequently* (Streffer; Gu)
  - with effect observed *even with 0.1 Gy*

- Similar observations with chemicals

Irradiation during the Implantation period (day 6-12) (incl. gastrulation)

- current view: no congenital malformation
- research on normal animals: shows a critical window: hypersensitivity to DNA-damage during gastrulation (vigorous apoptosis already at 0.05 cGy) (Heyer, Baatout) This is a welcome protection against damaged cells (altruistic suicide).

Irradiation during the Implantation period (day 6-12) (2)

- research on **Genetic susceptible** mice (p53):
  - p53 - - (no p53 related apoptosis) : cong. malf. in controls, more congenital malformations after irradiation, sometimes not lethal
  - p53 +- (Li-fraumeni-like): more **cong. malf**., sometimes not lethal (less than p53--)
- mechanism: in these observations, the cause of the congenital malformation is not an increased loss of cells (classic deterministic effect) but rather the persistence of **unrepaired or misrepaired DNA-damaged cells**.

In utero irradiation and role of **other genes** involved in **DNA-damage response** (all phases of pregnancy)

– gastrulation seems to be the critical period;

– most homozygote embryos die;

– *lack of observations with heterozygotes*

Precautionary lecture

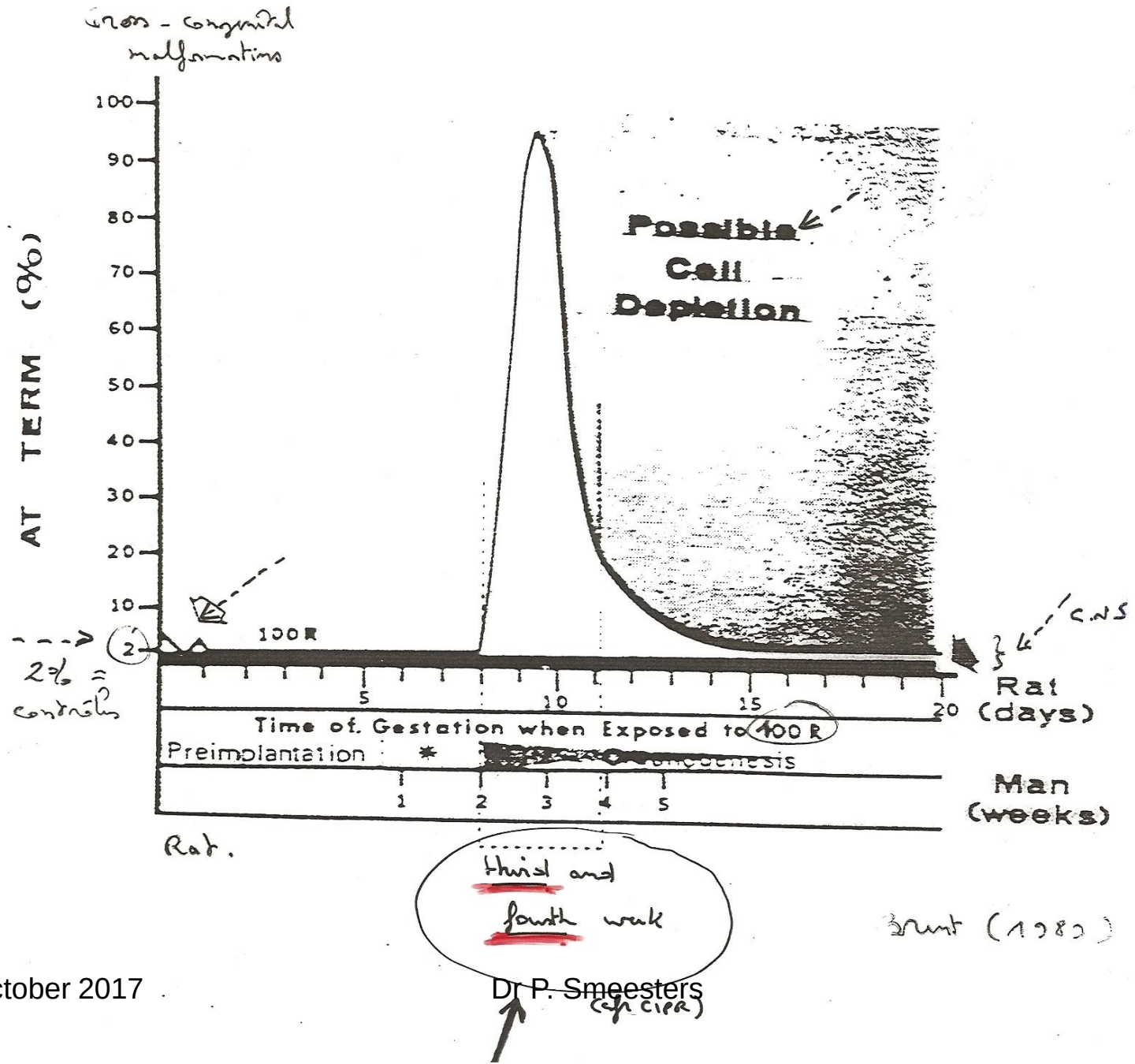
(*2001 RIHSS Scientific Seminar; 2011 SCK/FANC Symposium)*

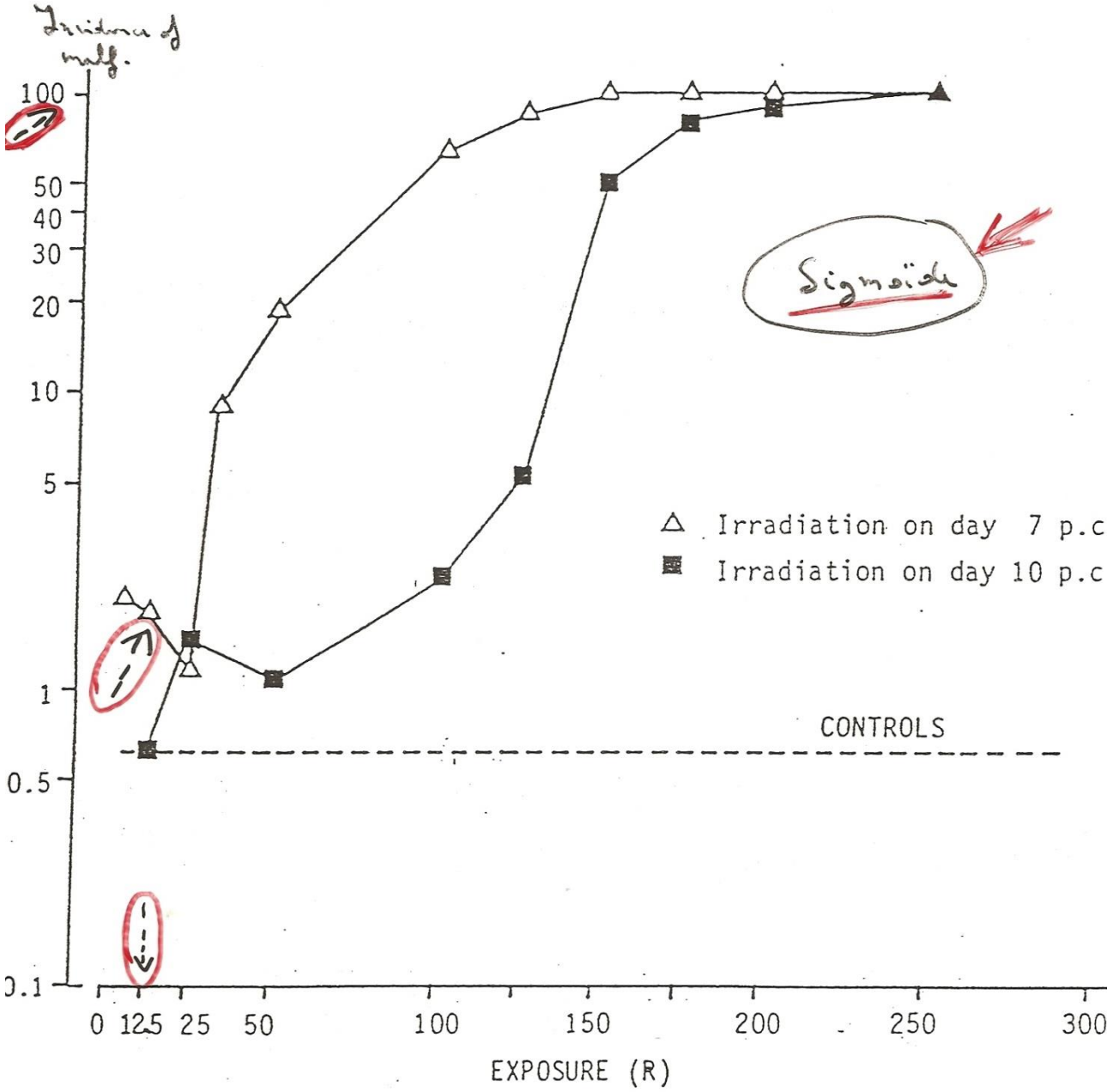
In humans, the same genetic susceptibilities probably exist.

If the mechanisms are similar (persistence of mis-repaired DNA-damaged cells), it is plausible that human genotypes leading to cancer-proneness are also associated with a genetic susceptibility to the radiation-induction of congenital abnormalities (or more subtle tissue dysfunctions).

The thresholds could be different,

or …..absent at day 1.


Gross - congenital malformations
AT TERM (%)
100
90
80
70
60
50
40
30
20
10
2
2% = controls
100 R
Possible Cell Depletion
CNS
Rat (days)
5
10
15
20
Time of Gestation when Exposed to 100 R
Preimplantation
Organogenesis
Man (weeks)
1
2
3
4
5
Rat.
third and fourth week
Brunt (1980)
(Ch CIPR)



...re ... The incidence of gross malformations in the mouse skeleton after various exposures on days 7 or 10 p.c.

Irradiation during Organogenesis (day 13 to 56~60):

- current view: congenital malformation possible above 0.1 Gy (too much cell loss)
- Research on **Genetic susceptible** mice (Norimura, Nomoto): p53
  - p53 - - (no apoptosis) : more congenital malforlmations, including not lethal ones
  - p53 +- (Li-fraumeni-like): **more** cong. malf., including not lethal ones(less than p53--)
  - protracted exposure (Kato): doesn't protect p53-- !
- mechanism: in these observations, the cause of the congenital malformation is not an increased loss of cells (classic deterministic effect) but rather **unrepaired or misrepaired DNA-damaged cells.**

Birth defects after Chernobyl: new data

(2011 EC Radiation Protection 170)

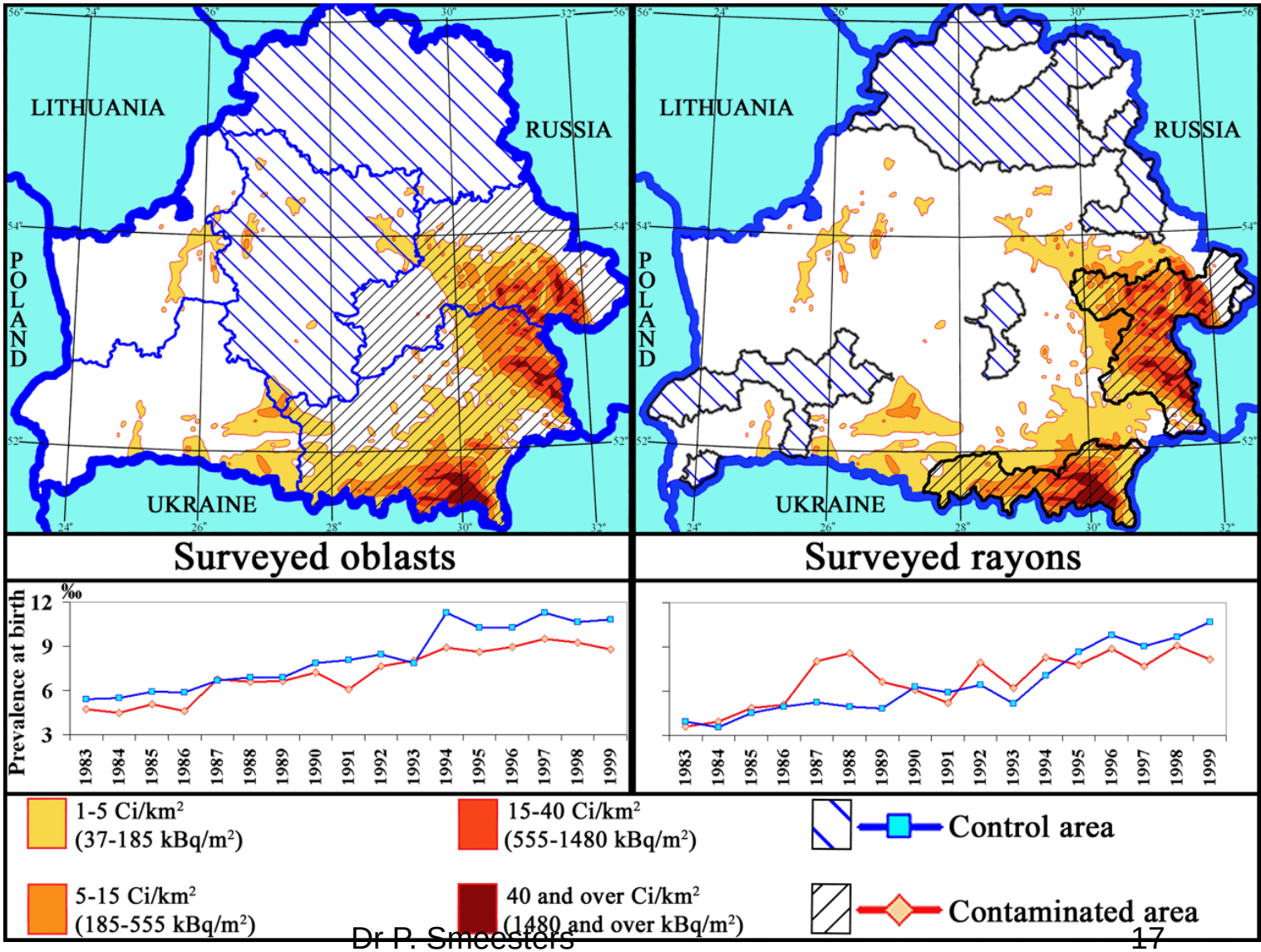
- not dealt with in UNSCEAR 2011
  - Reason: prevalence at birth of the malformations recorded in the registry in Belarus: similar positive trend in areas of low and high contamination
- Brussels 2006 Symposium, Budapest 2007 Eurocat workhop :
  - **From oblasts to districts**
  - Clear excess of the congenital anomalies under study in the highly contaminated districts ***during the three first years*** (mainly polydactyly, reduction defects of limbs, multiple congenital malformations)

Prevalence at birth of 9 mandatory registered congenital anomalies in the areas contrasting by radionuclide contamination

1. Anencephaly *
2. Spina bifida
3. Cleft lip and (or) palate
4. Polydactyly *
5. Reduction defects of limbs *
6. Oesophageal atresia (stenosis)
7. Rectal atresia (stenosis)
8. Down's syndrome
9. Multiple congenital malformations *

12,167 cases in 4 oblast

2,189 cases in 47 rayons



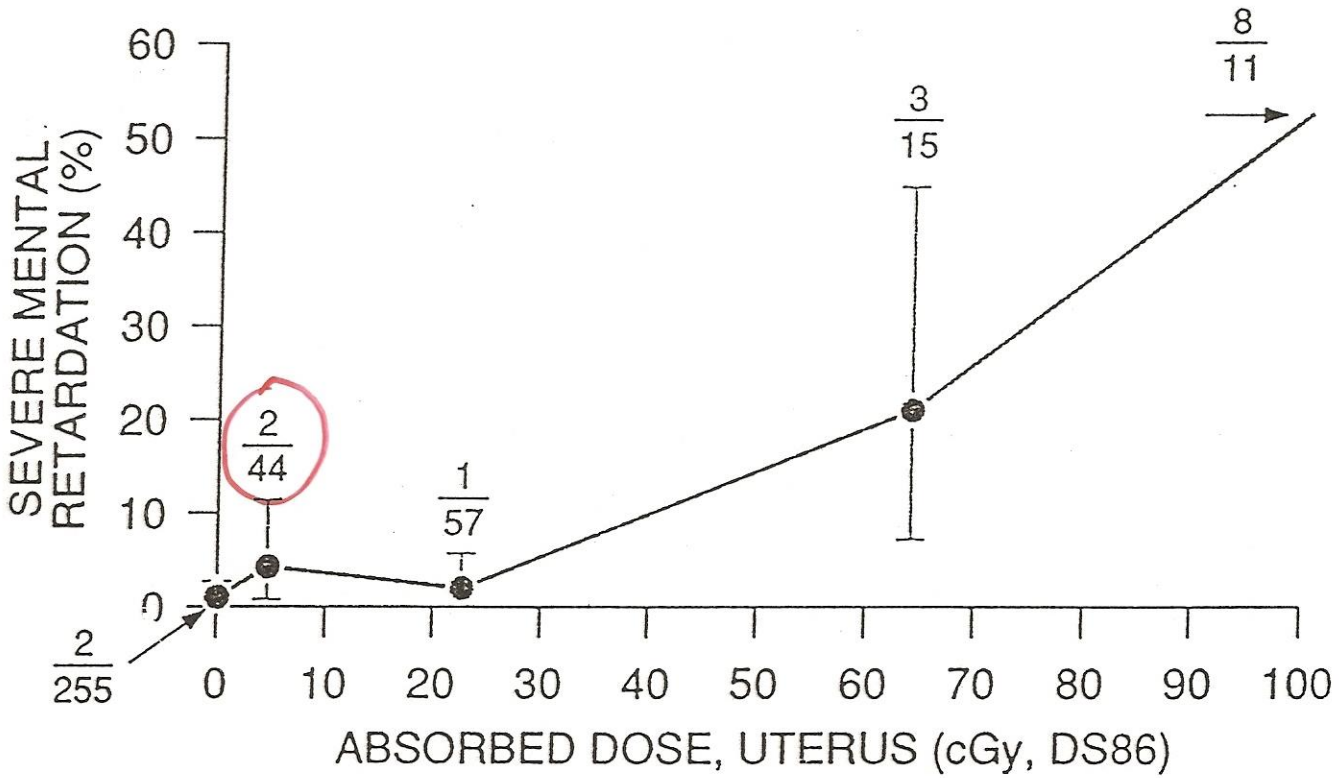
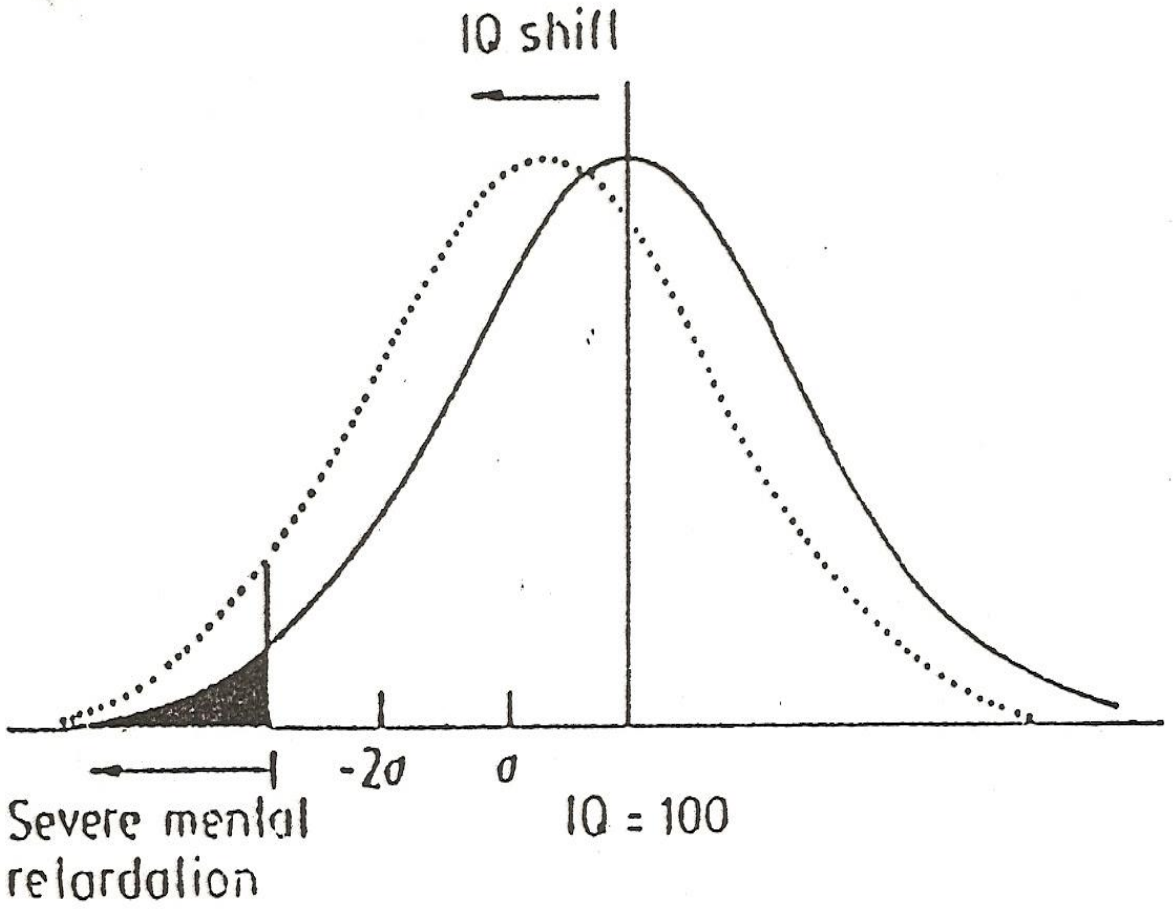


Fig. 12.4 Frequency of severe mental retardation, as a function of uterine dose, in children irradiated at gestational age between 8 to 15 weeks. Data from Hiroshima and Nagasaki are pooled, but the cases of Down syndrome are excluded (from Otake *et al.*, 1988a).

FIGURE 3 Representation of the downward shift of IQ following irradiation *in utero*

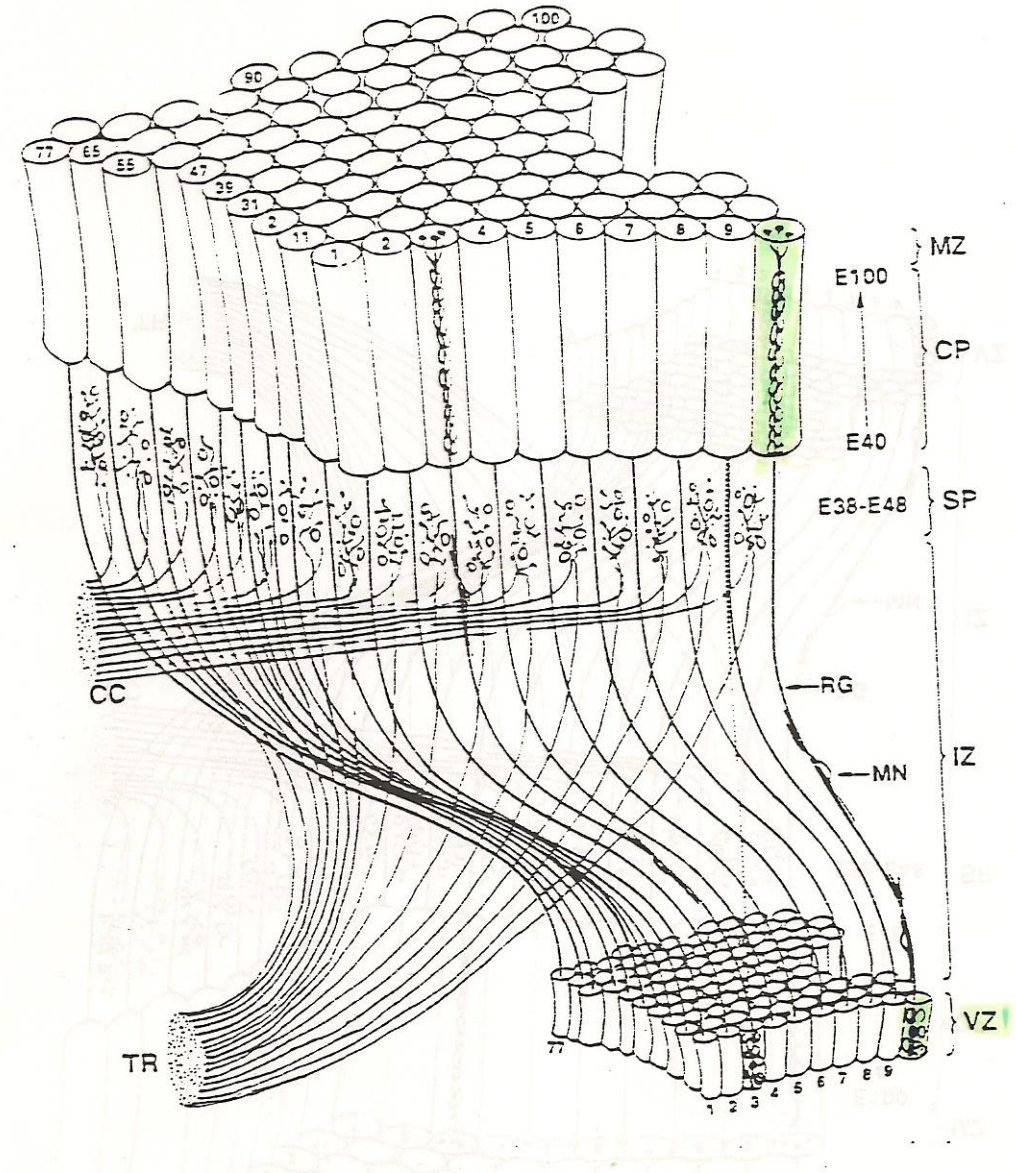


NCS effects

. Neuronal mortality

- Migration perturbations (NMR)

- Synaptic errors


MZ
E100
CP
E40
E38-E48
SP
RG
MN
IZ
VZ
CC
TR

Irradiation in utero in NCS phase: current views and statements: again the 100 mSv break-point

8 -25 weeks post-conception:

- Severe mental retardation above threshold dose (lower confidence limit A-bomb study: 300 mGy)
- Lower IQ: "Under 100 mGy, any effect on IQ would be of **no practical significance** "(ICRP 103)"

100 mGy? ICRP 90: more nuances

8 - 25 weeks post-conception: Lower IQ:

- 8-15 w: Linear radiation dose response (21 IQ points/Gy)
- 16-25 w: LQ dose response (13 IQ points/Gy)
- a threshold dose is not apparent

Effects of prenatal exposure: still major open questions (cfr ICRP 90)

- « Data from human studies with protracted exposures are almost nil »
- « High-LET radiation and incorporation of radioactive substances: virtually no data available from human studies »
- « Prenatal exposures and chronic mental deficiencies: completely open field that should be studied » ……

FP7 CEREBRAD (Cognitive and Cerebrovascular Effects Induced by Low Dose Ionizing Radiation)

- European consortium including radiobiologists, epidemiologists, neurobiologists, bio-informaticians, paediatricians and dosimetrists

- two approaches: (1) a direct health assessment through epidemiological studies on exposed individuals (Chernobyl, hemangiomas, childhood radiotherapy)and (2) investigation of dose-dependent biological effects using a mouse model

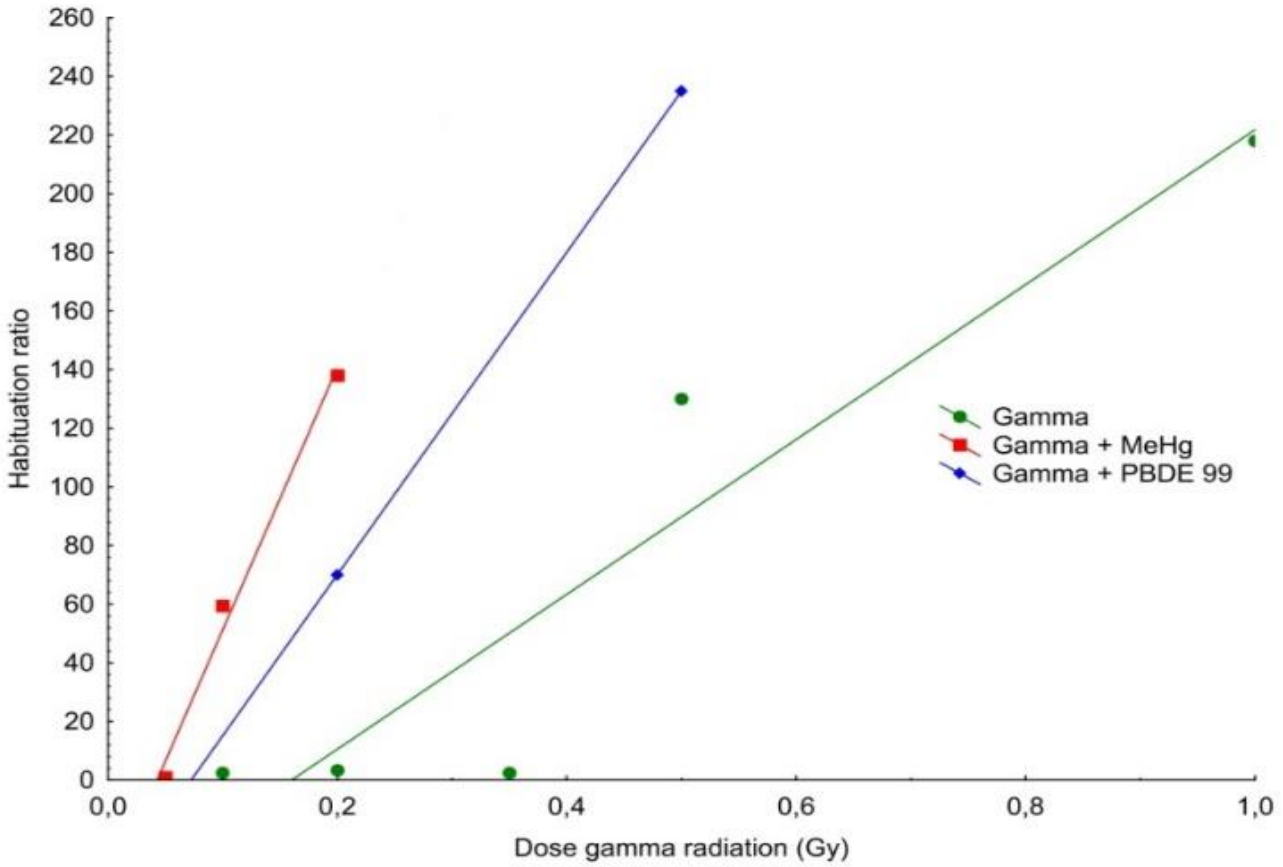
Main results:
Human studies at LD

Regarding cognitive outcome, a threshold dose in the range of 50 to 120 mGy was evidenced for the hemangioma cohort consisting of 115 subjects treated before the age of one year and receiving (much!) less than 1 Gy to the brain.

Main results (animal studies)

- Cognitive defects : dose-related; similarly affected in in utero and PND10 exposed animals; for subtle function, a low dose of external IR (0.1 Gy) already showed effects

- Combined effects: at PND10, interaction of ionising radiation with other toxicants (that may be present in the daily environment nicotine, methylmercury, the pesticide Paraquat or the flame retardant pentabromodiphenyl ether): lowering of the threshold dose below 0.1 Gy + change of slope of DR curve


Habituation ratio
260
240
220
200
180
160
140
120
100
80
60
40
20
0
0,0
0,2
0,4
0,6
0,8
1,0
Dose gamma radiation (Gy)
Gamma
Gamma + MeHg
Gamma + PBDE 99

Long-lasting effects

- Brain structure and function deficits (cognition, cell death and neurogenesis): after prenatal irradiation from 0.1 Gy
- Molecular and cellular changes up to 24 weeks after irradiation: strongly suggest that LD-IR might influence natural ageing (and neurodegenerative diseases)
- Transcriptomic and proteomic analyses indicate possible contribution of epigenetic events in the processing of the late effects

A new cross-cutting issue: IR-induced epigenetic alterations

- without DNA mutation
- DNA-methylation, histone modifications, micro-RNAs
- linked to the induction and persistence of IR-induced genomic instability
- Concern all effects: cancers, non-cancer diseases and hereditary/transgenerational effects.

Medically exposed groups and Japanese atomic bomb survivors: childhood leukaemias

- OSCC (Oxford Survey of Childhood Cancers) and all other case-control studies: association childhood leukaemia and antenatal X-ray exam.
- Many of the objections to a cause-and-effect explanation now been met
- Not compatible with Japanese atomic bomb survivors but:
  - Follow up Japan commenced in 1950! Lost cases or not recognized cases
  - Ohtaki et al (2004)

Ohtaki 2004

- No increase with dose of the frequency of stable chromosome translocations in the blood lymphocytes of the survivors irradiated *in utero*.
- Increase in translocations with dose found for some of the mothers.
- An interpretation of this finding is that the haematopoietic system *in utero* is particularly sensitive to radiation-induced cell killing, which would imply that moderate and high acute doses of radiation received *in utero* do not materially increase the subsequent risk of childhood leukaemia, a potential explanation for the absence of cases of childhood leukaemia among the Japanese atomic bomb survivors irradiated *in utero*.

In utero irradiation and cancer

- BEIR VII: « Studies of prenatal exposure to diagnostic X-rays have, despite long-standing controversy, provided important information on the existence of a significantly increased risk of **leukaemia and childhood cancer** following diagnostic doses of **10-20 mGy** in utero »

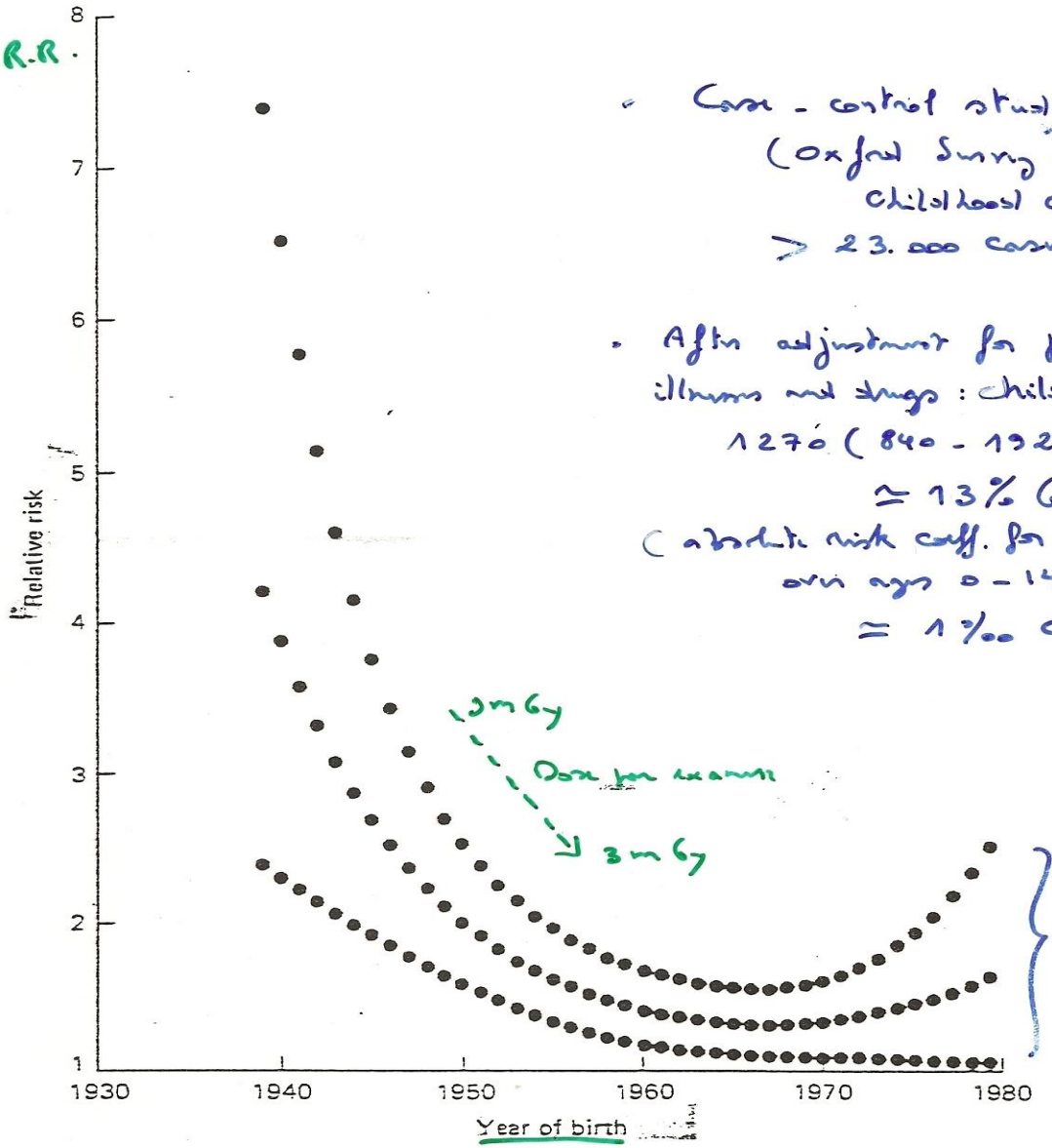


Figure 29.1 X-ray related relative risk of childhood cancer following prenatal X-ray. Based on analysis of deaths during 1953–1979. (Upper and lower plots show 95% confidence limits.)

Whole pregnancy: cancer induction

- Embryo and fetus more sensitive
- Cancers appear in first 10 y or later
- No threshold dose
- Risk dose-related (fatal cancers): LNT
  - 10 mSv : 1-2/1000
  - 100 mSv : **1-2/100**

Some examples!

Radiological examinations

(N. Buls, UZ Brussel, fœtal dose for complete examination)

Natural background: 2 mSv/y (low dose rate!)

- Thorax: <0,01 mSv
- Abdomen: 3 mSv
- Urographie intra-veineuse: 7 mSv
- CT abdomen (scanner): 25 mSv
- CT rachis lombaire (scanner): 39 mSv

Differences in doses up to a factor of 10

frequent in existing international investigations

(Low dose) irradiation in utero: concerns

There are **still many uncertainties** (genetic susceptibilities, long term effects due to modification of gene expression, internal chronic exposures, subtle effects or long term effects of NCS irradiation….)

But: **Few research! Few labs! ; lack of budget; statistical limitations** (small numbers of animals; cost of KO animals)

Planned situations v/ existing situations

- Ethical implications and attitudes totally different
- Planned situations: exposure often avoidable, otherwise ALARA
  - Apply the Precautionary principle if possible
  - Absence of (hard) evidence (of harm) is not evidence of absence
- Existing situations: (accidental) exposure of pregnant woman has occurred : no panic
  - Evaluate the dose and the risk, with the uncertainties
  - Informed decision: responsibility principle