Etiologie des leucémies de l'enfant – Présentation des études initiées par BfS

Bernd Grosche, Gunde Ziegelberger
Anne Dehos, Sabine Hornhardt
Federal Office for Radiation Protection
Germany
bgrosche@bfs.de

Background

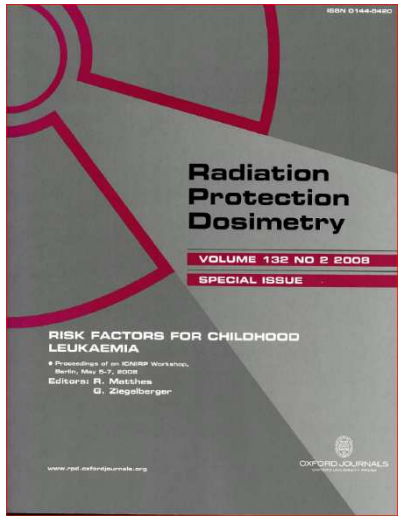
- Slightly elevated risk for childhood leukaemia amongst those aged below 5 years
  - magnetic fields above 0,3-0,4 µT
  - living near NPPs (KiKK Study)
- Observation cannot be explained by current knowledge on such low exposures
- Slow but constant increase of incidence rates

ICNIRP/WHO/BfS International Workshop on Risk Factors for Childhood Leukemia

Berlin, May 2008

Potential Causes of Childhood Leukemia

- Genetic - yes
- Ionizing Radiation - yes
  - Nuclear power plants ?
  - Radon Gas ?
  - X-rays ?
- Non-ionizing Radiation - hmm
  - ELF-EMF - nice association
  - RF-EMF ?
- Chemicals - nothing jumps out
  - Air pollution
  - Smoking
  - Pesticides/herbicides
  - POPs
  - Maternal solvent - maybe
- Socioeconomic factors - ???
- Birth weight - no, it's growth
  - Maternal diet
    - Topoisomerase inhibitors
  - Nutrition
  - Growth factors
  - Folate
- Immune Status
  - Breastfeeding
  - Childcare
  - Etc.



(Summary by C. Portier 2008, RPD)

"Given the current knowledge and the relative risks seen in the numerous epidemiology studies of childhood leukaemia, my best estimate is that **the attributable fraction has been accounted for by < 10%**. This means that, for more than 90% of the cases, there is no known or even suggested cause."

Two relevant workshops

2010, Hohenkammer, Germany
Organized by BfS

Citation: Blood Cancer Journal (2011) 1, e1; doi:10.1038/bcj.2010.1

www.nature.com/bcj

MEETING REPORT

Research recommendations toward a better understanding of the causes of childhood leukemia

G Ziegelberger[1], C Baum[2], A Borkhardt[3], C Cobaleda[4], C Dasenbrock[5], A Dehos[1], B Grosche[1], J Hauer[3], S Hornhardt[1], T Jung[1], T Kammertoens[6], I Lagroye[7], H Lehrach[8], T Lightfoot[9], MP Little[10], C Rossig[11], I Sanchez-Garcia[12], M Schrappe[13], J Schuez[14], S Shalapour[6], R Slany[15], M Stanulla[13] and W Weiss[1]

[1]Department of Radiation and Health, Federal Office for Radiation Protection (BfS), Oberschleissheim, Germany; [2]Department of Experimental Hematology, Hannover Medical School, Hannover, Germany; [3]Department of Paediatric Oncology, Haematology and Clinical Immunology, Center for Child and Adolescent Health, Heinrich Heine University, Duesseldorf, Germany; [4]CBMSO, Spanish Research Council (CSIC), Universidad Autonoma, Madrid, Spain; [5]Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM), Hannover, Germany; [6]Institute of Immunology and Department of Paediatric Oncology and Haematology, Charite Universitaetsmedizin, Berlin, Germany; [7]Laboratoire IMS UMR 5218, University of Bordeaux, Bordeaux, France; [8]Max Planck Institute for Molecular Genetics, Berlin, Germany; [9]Department of Health Sciences, Epidemiology & Genetics Unit, University of York, York, UK; [10]Radiation Epidemiology Branch, National Cancer Institute, Rockville, MD, USA; [11]University Children's Hospital Muenster, Pediatric Hematology and Oncology, Muenster, Germany; [12]IBMCC, Spanish Research Council (CSIC), University of Salamanca, Salamanca, Spain; [13]Department of General Paediatrics, University Medical Center Schleswig-Holstein, Kiel, Germany; [14]Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France and [15]Department of Genetics, Friedrich Alexander University, Erlangen, Germany

Blood Cancer Journal (2011) **1**, e1; doi:10.1038/bcj.2010.1; published online 28 January 2011

A small expert group met in conclave in July 2010 to define a long-term strategic research agenda toward further clarification of the etiology of childhood leukemia (CL). The motivation and invitation for this project came from the German Office for Radiation Protection (BfS) because radiation experts have been puzzled for some time by epidemiological findings of an

Incidence rates and epidemiological findings

The reported increasing incidence rates seen for B-cell precursor ALL (but not for T-ALL or acute myelogenous leukemia (AML)) in industrialized countries[4] point toward a role for the modern lifestyle. However, to date, epidemiological studies have failed to confirm any associations with lifestyle exposures such as smoking, alcohol, diet, social status, and so on. Indeed, to date, the only recognized risk factors for ALL are heavy birth weight[5,6] and gender, with boys more often affected than girls (approximate ratio 1.2:1).—*However, the validity of these*

(Ziegelberger et al 2011, BCJ)

Conclusion and Research Recommendations

- Further research needed into the causes of childhood leukaemia
  - Human studies
  - Genetic studies
  - Animal studies
- What is the pathogenesis of childhood leukaemia?
- How do the various factors interact?

Two relevant workshops

2012, Bombon, France
Organized by IRSN & BfS for MELODI

OPEN ACCESS
IOP Publishing | Society for Radiological Protection
Journal of Radiological Protection
J. Radiol. Prot. **34** (2014) R53–R68
doi:10.1088/0952-4746/34/3/R53

Review

Childhood leukaemia risks: from unexplained findings near nuclear installations to recommendations for future research

D Laurier[1,12], B Grosche[2], A Auvinen[3], J Clavel[4], C Cobaleda[5], A Dehos[2], S Hornhardt[2], S Jacob[1], P Kaatsch[6], O Kosti[7], C Kuehni[8], T Lightfoot[9], B Spycher[8], A Van Nieuwenhuyse[10], R Wakeford[11] and G Ziegelberger[2,*]

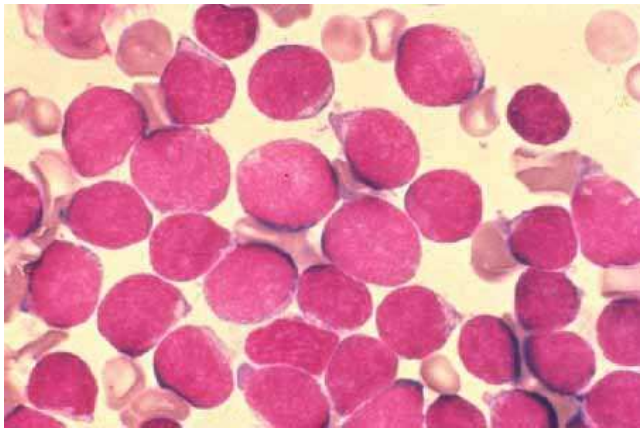
[1] Institut de Radioprotection et de Sûreté Nucléaire (IRSN), BP 17, F-92262 Fontenay-aux-Roses Cedex, France
[2] Federal Office for Radiation Protection (BfS), Ingolstaedter Landstr. 1, D-85764 Neuherberg, Germany

(Laurier et al 2014, JRP)

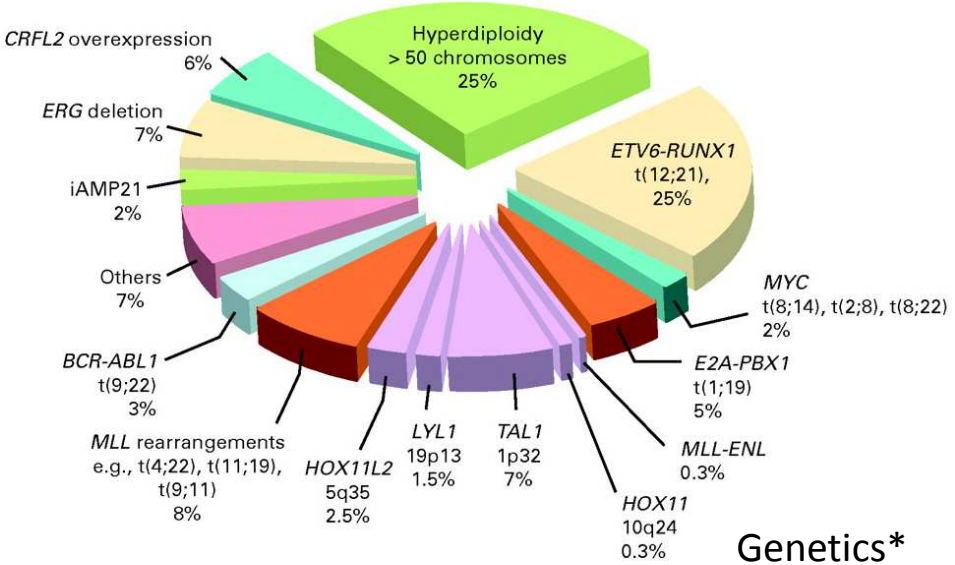
2012 Workshop: Conclusions and Recommendations

- Continuous surveillance of childhood leukaemia incidence
- No specific epidemiological study for vicinity of NPPs
  - needed: prior hypotheses, accurate exposure estimates, no major biases
  - If still so: link to research into the pathogenesis and collection of bio-specimens
- Harmonise exposure estimates (probably including incorporated radionuclides) and characterise the population (SES, environment)
- Distinguish between leukaemia subtypes
- Foster international collaboration
- Prevalence of the preleukaemic clone (ETV6-RUNX1 and other translocations)
- Role of the immune function *(Kinlen hypothesis?)*
- Use of animal models

ALL: a heterogenous disease

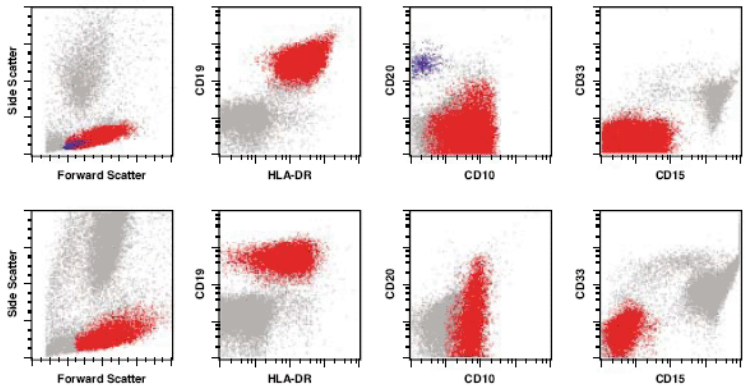


Morphology

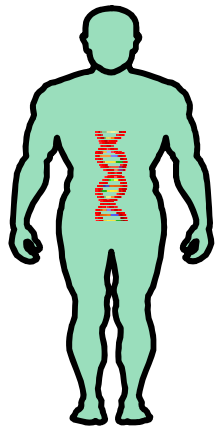


Genetics*

*Pui et al. 2011, JCO



Immunology



Host factors

BfS Pilot studies

1. Investigation on the prevalence of potentially predisposing chromosomal translocations
2. Deep sequencing and bioinformatic analysis of pediatric ALL cases
3. Feasibility of establishing a birth cohort in Germany
4. Comparison of incidence rates in different countries world wide
5. Animal models applicable for research on childhood leukaemia

Investigation on the prevalence of potentially predisposing chromosomal translocations

(Elisa Füller, Daniel Schäfer, Ute Fischer, Pina F.I. Krell, Martin Stanulla, Arndt Borkhardt and Robert Slany)

Frequency of preleukaemic clones in newborns

Comparison of the prevalence in populations with different incidence rates

Hurdle: reliable detection of rare preleukaemic clones

→ Development of validated PCR primers

Deep sequencing and bioinformatic analysis of pediatric ALL cases

(Charité, Berlin; EMBL, Heidelberg; Max-Planck-Institute of Molecular Genetics, Berlin; University Hospital, Düsseldorf; University Hospital Schleswig-Holstein, Kiel; Hannover Medical School; (University Hospital, Zurich))

Deep sequencing can focus on detailed differences and mutations

These could, at least in part, reflect the effects of the environment

Could help to detect common patterns/footprints possibly correlated to external risk factors

Feasibility of a German birth cohort

(Hajo Zeeb and co-workers)

Pilot to test the feasibility of a birth cohort study in Germany, incl. sampling and storage of cord blood.

Comparison of incidence rates in different countries world wide

Tracy Lightfoot, Friederike Erdmann, Joachim Schüz

Pilot to develop a main study protocol for a multinational study of childhood leukaemia investigating the potential aetiological roles of genetic pre-disposition, biomarkers of infectious exposure and selected environmental factors

Animal models

(Arndt Borkhardt, Isidro Sanchez-Garcia, Cesar Cobaleda, Julia Hauer)

The ultimate goal is to be able to mimic in the mouse the entire molecular, cellular, tissue and organic features of human B-cell ALL, including its initiation, progression, evolution, response to therapy and eventual cure or relapse.

Conclusion

- Interdisciplinary cooperation has shown new ways forward, and the results from the pilot studies – though not yet completely published in the open literature – have shown that such large studies with a broader approach are capable to give new insights into pathogeneis and the causes of childhood leukaemia.

Merci beaucoup!