Childhood leukemia and environmental factors

Health Council of the Netherlands

Superior Health Council Belgium

EuSANH

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To
the Minister of Health, Welfare and Sport of the Netherlands
the Minister of Social Affairs and Public Health of Belgium

Subject	: presentation of advisory report *Childhood leukaemia and environmental factors*
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Dear Ministers,

Although the treatment of childhood leukaemia has made progress in recent decades, the occurrence of this serious disease tends to raise concerns about the possibility of environmental causes. An extensive evaluation of the scientific knowledge shows in general limited evidence for causal relations with specific environmental factors. The disease occurs through a complex interplay of genetic susceptibilities and different environmental factors that is hard to unravel.

This is the main conclusion of the advisory report that we are pleased to present to you. It has been drafted by a joint Committee of the Belgian Superior Health Council and the Health Council of the Netherlands, and has been reviewed by experts connected to both councils as well as by experts from the European Science Advisory Network for Health (EuSANH).

In the last decade of the 20th century the incidence of childhood leukaemia has shown an increase, raising the question what role environmental exposures have played in this. The trend now seems to have been stopped or even reversed, but there are still approximately 80 new cases of childhood leukaemia per year in Belgium and about 140 new cases in the Netherlands.

The possibilities to reduce these numbers are limited, since few environmental factors could be identified as contributors. Most cases of childhood leukaemia simply cannot be prevented. The report does, however, suggest a few protective measures and health recommendations, given the available evidence and the importance of a precautionary approach when much is still uncertain. The application of precautionary measures is required more in the case of some factors than in others, depending on, among other considerations, what is known.

In view of the relatively small numbers of cases of childhood leukaemia per country, the councils recommend international cooperation in studying variations in the incidence of childhood leukaemia and their possible relations to different environmental exposures. Cooperation is also recommended in studying possible interactions between different agents and genetic subtypes linked to the onset of childhood leukaemia.

This is the first advisory report that is the result of a collaborative effort within the framework of EuSANH. Both councils hope it will not prove to be unique. The collaboration has resulted in an evaluation of the scientific evidence that is fully agreed upon by the two health councils.

One of the goals of EuSANH is to provide science based policy advice that transcends national boundaries, in order to prevent duplication of work and to arrive at shared insights. This will not only have financial benefits, but also provide a more solid basis for national and international policies. It is our hope that this report will help to realise these aims.

Yours sincerely

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Childhood leukaemia and environmental factors

to:

the Minister of Health, Welfare and Sport of the Netherlands

the Minister of Social Affairs and Public Health of Belgium

The Health Council of the Netherlands is an independent scientific advisory body. It is our task to provide the government and Parliament with advice in the field of public health and health/healthcare research.

The Superior Health Council of Belgium is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment.

The Health Council of the Netherlands and the Superior Health Council of Belgium are members of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

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Executive Summary

Childhood leukaemia is a cancer that affects the blood forming system in the body. The disease is caused by a complex interplay of genetic, natural and man-made environmental factors. In Belgium, the Netherlands and other Northwestern European countries each year about 5 in 100,000 children are confronted with this serious condition, which requires intensive treatment. In recent years the average number of new cases per year was approximately 80 in Belgium and 140 in the Netherlands.

Most young patients have a lymphoid type of acute leukaemia, ALL. A smaller percentage is affected by an acute myeloid manifestation of the disease, AML. Due to the improvements in care and treatment in recent decades in Western-European countries, about 85% of children with ALL and about 60% of children with AML survive the first five years after they have been diagnosed.

In the last decade of the 20th century the occurrence of childhood leukaemia has shown a rise. The question arose whether this could be attributed to an increased exposure to risk factors. Although this trend now seems to have been stopped or even reversed, there is still every reason to get more clarity on the role of environmental factors in the induction and development of childhood leukaemia.

It is the aim of this report, drawn up by a joint Committee of the Belgian Superior Health Council and the Health Council of the Netherlands, to do just that. The Committee has taken a precautionary perspective to guide its evaluation of scientific knowledge and recommendations.

Evidence on the impact of environmental factors

The complex interplay of genetic abnormalities and natural and man-made environmental exposures makes it hard to establish the role of separate factors. Based on current knowledge, the most important conclusions are that the majority of leukaemia cases cannot be explained and only a small fraction of cases might be prevented. Those are addressed in this report.

Only where ionising radiation is concerned, a causal relation with childhood leukaemia has been established. Exposure to this type of radiation occurs naturally, but also through medical applications such as X-rays and in particular CT-scans.

For exposure to benzene and tobacco smoking of fathers a causal relationship with childhood leukaemia is deemed likely, given the available evidence. A

relation with pesticides is labelled ‘possible to likely’. Two protective influences are also considered likely: breast feeding and day-care attendance or other contacts between young children.

For the majority of physical, chemical and other environmental factors under study, the likelihood of a causal relation with the onset of childhood leukaemia could only be labelled as ‘possible’, ‘uncertain’ or ‘unknown’.

Recommended measures

In view of the findings in this report, the Committee advocates to complement the traditional anti-microbial hygiene with ‘physical-chemical hygiene’, aiming to limiting environmental exposures to possibly harmful agents as much as feasible.

Given the tentative nature of much of the scientific knowledge and the limited possibilities to reduce the role of naturally occurring exposures, only a limited array of measures are (as yet) available to limit possibly harmful exposures or to utilise protective opportunities. In this, a balance needs to be struck between sufficient precaution and being overly careful.

Some principles are, however, clear. The median age for the onset of childhood leukaemia is around five. To be effective, measures will therefore have to be primarily aimed at pre-school children, infants, pregnant women and women (and their partners) intending to conceive. The Committee recommends that women of childbearing age should be counselled, in order to create awareness of the risk of certain environmental and lifestyle factors previous to an intended conception. Furthermore, with this much still uncertain, it makes sense to suggest measures that are in accordance with policies and guidelines that have already been implemented to protect against other diseases or risks.

Within these parameters, a number of recommendations can be given:

- Priority should be given to reducing the exposure to ionising radiation for medical purposes in the case of pregnant women and young children. More risk awareness among professionals in choosing diagnostic methods can achieve this.
- Although a causal relation with the currently used exposures to ultrasound scans that are routinely made during pregnancy is considered unlikely, ultrasound scans should not be offered without medical indication, to limit exposure.
- An important measure is the reduction of exposure to pesticides, especially for pregnant women who may be exposed in the work place or at home, and for women who wish to conceive. They should refrain from working with pesticides, or use extra protective measures.
- Since smoking (both of tobacco and marijuana) and alcohol use by parents are known to be able to contribute to several adverse health effects in

children, guidelines regarding these lifestyle factors are already in place. Although a causal relation with childhood leukaemia has not been established, the possibility of such a relation may give extra credence to the current advice to refrain from these activities, especially while trying to conceive and during pregnancy.

- It is also advisable, given the possibility of a causal relation with childhood leukaemia, for pregnant women to avoid nitrite-cured meat, such as ham, bacon and sausages.
- Finally, the existing recommendation to breast-feed up to the age of six months, whenever it is feasible to do so, is reinforced by the likelihood that breast feeding may also protect against childhood leukaemia.

A need for further knowledge

Although more knowledge has been emerging, many things about the environmental causes of childhood leukaemia are as yet uncertain or only tentatively understood. The findings in this report, however, clearly indicate where further research is most needed.

Since the numbers of patients per country are often too small to establish relationships between causes and effects, international studies on the incidence of childhood leukaemia and its relation to environmental factors are required. At the same time, research into specific factors, particularly the adverse effects of frequent ultrasounds and the use of pesticides, need to be carried out. In addition, research is needed into the accumulation of risks due to combined exposures, since this subject has so far hardly been explored.

Samenvatting

Leukemie bij kinderen is een vorm van kanker in het bloedvormende systeem van het lichaam. De ziekte wordt veroorzaakt door een complex samenspel van genetische factoren en omgevingsinvloeden (zowel natuurlijke als door de mens geproduceerde). In België, Nederland en andere landen in Noordwest Europa worden elk jaar 5 op de 100.000 kinderen getroffen door deze ernstige aandoening, die een zware behandeling vergt. Het gemiddelde aantal nieuwe gevallen per jaar lag recent rond de 80 in België, en rond de 140 in Nederland.

Het grootste deel van de jonge patiëntjes lijdt aan acute lymfatische leukemie (ALL). Een kleiner percentage heeft acute myeloïde leukemie (AML). Dankzij de verbeteringen in behandeling en zorg die de afgelopen decennia in West-Europese landen zijn gerealiseerd, overleeft zo'n 85% van de kinderen met ALL de eerste vijf jaar na de diagnose, en circa 60% van de kinderen met AML.

In het laatste decennium van de 20e eeuw heeft de incidentie van kinderleukemie een stijging laten zien. De vraag kwam daarbij op of dit kon samenhangen met een verhoogde blootstelling aan schadelijke omgevingsfactoren. Hoewel de trend nu gestopt lijkt te zijn of zelfs gekeerd, is er nog steeds alle reden om meer helderheid te krijgen over de mogelijke rol van omgevingsfactoren bij het ontstaan en de ontwikkeling van kinderleukemie.

Dat is dan ook het doel van dit advies, dat is opgesteld door een gezamenlijke commissie van de Belgische Hoge Gezondheidsraad en de Nederlandse Gezondheidsraad. De commissie heeft zich bij haar evaluatie van de wetenschappelijke kennis en bij het formuleren van aanbevelingen laten leiden door het voorzorgprincipe.

Kennis over de invloed van omgevingsfactoren

Door het complexe samenspel tussen genetische afwijkingen en blootstelling aan natuurlijke en kunstmatige omgevingsfactoren is het lastig een helder beeld te krijgen van de rol die individuele factoren spelen. Op grond van de beschikbare kennis is de belangrijkste conclusie dan ook dat het merendeel van de gevallen van kinderleukemie niet verklaard kan worden, en dat slechts een klein deel te voorkomen zal zijn. Dit advies gaat over de mogelijkheden om binnen dat kleine deel een reductie te bewerkstelligen.

Alleen voor ioniserende straling is een oorzakelijk verband met kinderleukemie gevonden dat beschouwd kan worden als 'aangetoond'.

Blootstelling aan dit type straling komt van nature voor, maar ontstaat ook door medische toepassingen, zoals röntgenfoto's en in het bijzonder CT-scans.

Een verband tussen kinderleukemie en blootstelling aan benzeen is op basis van de huidige kennis beoordeeld als 'waarschijnlijk'. Voor het roken door ouders en blootstelling aan bestrijdingsmiddelen is het bestaan van een verband beoordeeld als 'mogelijk tot waarschijnlijk'. Verder zijn er twee beschermende invloeden die als 'waarschijnlijk' zijn gelabeld: het krijgen van borstvoeding en het bezoeken van een kinderdagverblijf of andere contacten tussen jonge kinderen.

Voor het merendeel van de fysische, chemische en andere omgevingsinvloeden die bestudeerd zijn kan het verband met kinderleukemie niet sterker worden aangeduid dan als 'mogelijk', 'onzeker' of 'onbekend'.

Aanbevolen maatregelen

Op basis van deze bevindingen adviseert de commissie om naast de traditionele microbacteriële hygiëne ook 'fysisch-chemische hygiëne' toe te passen, om zo de blootstelling aan mogelijk schadelijke omgevingsinvloeden zoveel mogelijk te beperken.

Vanwege het weinig robuuste wetenschappelijke bewijs en de beperkte mogelijkheden om de blootstelling aan natuurlijke invloeden te beperken, is er vooralsnog ook slechts een beperkte hoeveelheid maatregelen voorhanden om blootstellingen te reduceren of de mogelijkheden voor bescherming te benutten. Daarbij moet bovendien een evenwicht bewaard worden tussen voldoende voorzorg en te grote voorzichtigheid.

Een aantal uitgangspunten is echter duidelijk. De gemiddelde leeftijd waarop kinderen leukemie krijgen ligt rond de vijf jaar. Om effect te hebben moeten maatregelen daarom primair gericht zijn op peuters, zuigelingen, zwangere vrouwen en vrouwen (en hun partners) die zwanger willen worden. De commissie adviseert om vrouwen die zwanger willen worden te voorzien van informatie, zodat zij weten welke omgevings- en leefstijlfactoren schadelijk kunnen zijn. Verder ligt het in de lijn, nu nog zoveel onzeker is, om met de aanbevelingen aan te sluiten bij bestaand beleid en bij de richtlijnen die al zijn geformuleerd met het oog op het voorkomen van andere ziektes of risico's.

Binnen deze contouren kunnen de volgende aanbevelingen worden gegeven:

- Het is van belang om de blootstelling aan ioniserende straling voor medische doeleinden bij zwangere vrouwen en jonge kinderen te verminderen. Dit kan gerealiseerd worden wanneer medische professionals beter rekening houden met de risico's bij de keuze voor diagnostische methoden.
- Hoewel een oorzakelijk verband met de huidige blootstelling aan echo's die routinematig tijdens de zwangerschap worden gemaakt onwaarschijnlijk

wordt geacht, zouden echo's niet aangeboden moeten worden zonder medische indicatie, om zo de blootstelling aan ultrageluid te beperken.

- Een belangrijke maatregel is ook om de blootstelling aan bestrijdingsmiddelen te beperken, in het bijzonder voor zwangere vrouwen op het werk en thuis, en voor vrouwen die zwanger willen worden. Beide groepen zouden niet met bestrijdingsmiddelen moeten werken, of extra beschermingsmaatregelen moeten nemen.
- Aangezien roken (zowel van tabak als marihuana) en alcoholgebruik door ouders kunnen leiden tot diverse negatieve gezondheidseffecten bij kinderen, zijn op dat punt al richtlijnen geformuleerd. Een oorzakelijk verband van deze leefstijlfactoren met kinderleukemie is weliswaar niet aangetoond, maar de mogelijkheid van zo'n verband kan een extra reden zijn om van roken en alcoholgebruik af te zien, in het bijzonder in de periode voorafgaand aan de conceptie en tijdens de zwangerschap.
- Het is ook aan te raden, gegeven de onzekerheid over een oorzakelijk verband met kinderleukemie, dat zwangere vrouwen geen vlees eten dat is behandeld met nitriet, zoals ham, spek en worst.
- Tot slot bevestigen de bevindingen dat borstvoeding mogelijk beschermt tegen kinderleukemie het belang van de bestaande aanbeveling om, wanneer dat kan, borstvoeding te geven tot de leeftijd van zes maanden.

Noodzaak van meer kennis

Hoewel de wetenschappelijke kennis zich zeker ontwikkelt, is over het verband tussen omgevingsinvloeden en kinderleukemie vooralsnog veel onduidelijk of betrekkelijk onzeker. De bevindingen in dit advies laten duidelijk zien waar verder onderzoek nodig is.

Aangezien het aantal patiënten per land vaak te klein is om een verband tussen oorzaken en gevolgen aan te kunnen tonen, is internationaal onderzoek naar de incidentie van kinderleukemie en de relatie met omgevingsfactoren noodzakelijk. Tegelijk is specifiek onderzoek nodig, met name naar de nadelige effecten van het gebruik van bestrijdingsmiddelen en naar eventuele effecten van frequent gebruik van echo's. Ook moet onderzoek gedaan worden naar de stapeling van risico's als gevolg van meervoudige blootstelling; dat is een onderwerp dat tot dusverre nog nauwelijks aandacht heeft gekregen.

Résumé

La leucémie infantile est une forme de cancer affectant le système hématopoïétique du corps humain. La maladie est provoquée par l'interaction complexe de facteurs génétiques, naturels et environnementaux produits par l'homme. En Belgique, aux Pays-Bas et dans d'autres pays d'Europe du nord-ouest, 5 enfants sur 100.000 sont touchés chaque année par cette maladie grave, nécessitant un traitement lourd. Au cours des dernières années, le nombre moyen de nouveaux cas par an se situait autour de 80 en Belgique et de 140 aux Pays-Bas.

La plupart des jeunes patients souffrent de leucémie aiguë lymphoblastique (LAL). Un pourcentage plus faible est atteint de leucémie aiguë myéloblastique (LAM). Grâce aux améliorations apportées au traitement et aux soins dans les pays d'Europe de l'Ouest au cours des dernières décennies, quelque 85% des enfants atteints de LAL survivent durant cinq ans après le diagnostic et environ 60% des enfants atteints de LAM.

Le nombre de cas de leucémie infantile a présenté une augmentation durant la dernière décennie du 20ème siècle. La question qui se pose dès lors est de savoir si cette augmentation peut être corrélée à une exposition accrue à des facteurs de risque. Bien que cette tendance semble maintenant stoppée voire inversée, il n'en reste pas moins nécessaire d'obtenir plus de précision au sujet du rôle des facteurs environnementaux dans l'apparition et le développement de la leucémie infantile.

Le présent avis, élaboré conjointement par le Conseil Supérieur de la Santé de Belgique et le *Gezondheidsraad* des Pays-Bas, a donc pour objectif d'y parvenir. Cette commission mixte s'est basée sur le principe de précaution pour évaluer les connaissances scientifiques et formuler des recommandations.

Preuves concernant l'impact des facteurs environnementaux

En raison de l'interaction complexe entre anomalies génétiques et expositions à des facteurs environnementaux naturels et artificiels, il n'est pas facile de déterminer clairement le rôle joué par les différents facteurs. Sur base des connaissances disponibles, les principales conclusions sont donc que la plupart des cas de leucémie infantile ne peuvent s'expliquer et que seule une petite partie des cas pourra faire l'objet d'une prévention. Le présent avis traite des possibilités de parvenir à une réduction au sein de cette petite fraction.

Seules les radiations ionisantes présentent un lien causal considéré comme 'démontré' avec la leucémie infantile. L'exposition à ce type de rayonnements est présente dans la nature mais est également générée par des applications médicales telles que les radiographies et en particulier les CT-scans.

En l'état actuel des connaissances, un lien entre la leucémie infantile et l'exposition au benzène est considéré comme 'vraisemblable'. En ce qui concerne le tabagisme parental et l'exposition aux pesticides, l'existence d'un lien est jugée 'possible à vraisemblable'. En outre, deux influences protectrices sont qualifiées de 'vraisemblables': l'allaitement maternel et la fréquentation d'une crèche ou tout autre contact entre jeunes enfants.

Pour la majorité des facteurs environnementaux physiques, chimiques et autres étudiés jusqu'à présent, la vraisemblance du lien causal avec l'apparition d'une leucémie infantile ne peut être qualifiée que de 'potentielle', 'incertaine' ou 'inconnue'.

Mesures recommandées

Au vu des constatations reprises dans le présent rapport, la commission préconise d'appliquer, outre la traditionnelle hygiène antimicrobienne, également 'l'hygiène physico-chimique' afin de limiter autant que possible les expositions environnementales à des agents potentiellement nocifs.

Vu le manque de consistance de la plupart des connaissances scientifiques et le peu d'opportunités de réduire le rôle des expositions naturelles, les mesures disponibles en vue de limiter les expositions potentiellement nocives ou de mettre à profit les possibilités de protection sont encore peu nombreuses. Dans ce contexte, il est nécessaire de trouver un équilibre entre précautions suffisantes et prudence excessive.

Certains principes sont pourtant clairs. L'âge médian auquel apparaît la leucémie infantile est d'environ cinq ans. Pour être efficaces, les mesures devront dès lors viser principalement les enfants d'âge préscolaire, les nourrissons, les femmes enceintes et les femmes souhaitant être enceintes (et leurs partenaires). La commission recommande d'informer les femmes en âge de procréer afin qu'elles prennent conscience du risque que représentent certains facteurs environnementaux et comportementaux avant d'envisager toute conception. En outre, au vu des incertitudes qui subsistent, il est logique que les suggestions émises soient conformes à la politique et aux directives déjà implémentées dans le cadre de la protection contre d'autres maladies ou risques.

Dans les limites fixées par ces paramètres, les recommandations suivantes peuvent être formulées:

- Priorité doit être accordée à la réduction de l'exposition aux radiations ionisantes à des fins médicales chez les femmes enceintes et les jeunes enfants. Une meilleure prise en compte des risques par les professionnels lors du choix des méthodes diagnostiques permettrait d'y parvenir.

- Bien qu'un lien causal avec les doses d'exposition utilisées actuellement dans le cadre des échographies réalisées en routine durant la grossesse soit considéré comme invraisemblable, ces échographies ne devraient pas être proposées sans indication médicale afin de limiter l'exposition.
- Une importante mesure consiste à réduire l'exposition aux pesticides, en particulier pour les femmes enceintes susceptibles d'être exposées au travail ou à domicile et pour les femmes souhaitant procréer. Elles devraient s'abstenir d'utiliser des pesticides dans le cadre du travail ou appliquer des mesures supplémentaires de protection.
- Il est notoire que la consommation de tabac (et de marijuana) et d'alcool par les parents est susceptible d'engendrer divers effets néfastes sur la santé des enfants. Des directives existent donc déjà concernant ces facteurs comportementaux. Bien que le lien causal avec la leucémie infantile n'ait pas été établi, la possibilité d'un tel lien peut donner une crédibilité supplémentaire au présent avis qui encourage à s'abstenir de fumer et de boire, en particulier si l'on souhaite procréer et durant la grossesse.
- Il est également conseillé, vu l'incertitude concernant le lien causal avec la leucémie infantile, que les femmes enceintes évitent de consommer de la viande traitée au nitrite comme le jambon, le bacon et les saucisses.
- Enfin, la recommandation actuelle d'allaiter dans la mesure du possible jusqu'à l'âge de six mois se trouve renforcée par le fait que l'allaitement a probablement aussi un effet protecteur contre la leucémie infantile.

Nécessité de connaissances supplémentaires

Bien que les connaissances se soient développées, il subsiste beaucoup d'incertitude ou d'incompréhension quant aux causes environnementales de la leucémie infantile. Les conclusions du présent rapport montrent clairement les domaines dans lesquels des études complémentaires sont les plus nécessaires.

Le nombre de patients par pays étant souvent trop peu élevé pour établir un lien de cause à effet, des études internationales sur l'incidence de la leucémie infantile et son lien avec des facteurs environnementaux sont requises. Dans le même temps, des études doivent être menées concernant des facteurs spécifiques, en particulier les effets néfastes de l'utilisation de pesticides et tout effet potentiel de l'utilisation fréquente des ultrasons. Des recherches doivent en outre être réalisées quant aux risques cumulatifs dus à des expositions simultanées, un sujet qui, jusqu'à présent, n'a guère été étudié.

1 Introduction

1.1 Why this report?

What is the role of environmental factors in the onset of childhood leukaemia? This question has been the subject of a multitude of scientific studies. It has also been frequently discussed in the media and among concerned individuals. Given the increasing body of publications of different origin, it can be hard to keep track of the scientifically established knowledge about this important issue, and to consider measures based on sufficient evidence.

It is the aim of this advisory report to address the question of environmental influences on the induction and development of childhood leukaemia, using the best available and most recent scientific insights. To do so, the Belgian Superior Health Council (SHC) and the Health Council of the Netherlands (HCN) have engaged in a joint advisory process, initiated by paediatric oncologists in Belgium, operating within the framework of the European Science Advisory Network for Health (EuSANH).

Burden of disease and impact on society

Leukaemias are cancers of the haematopoietic (blood forming) system. Although rare, they are the most common malignancies in early childhood. During the last two decades of the past century, the average annual incidence* of all childhood leukaemias in Europe was 4.4 per 100,000 per year.[1]

Leukaemia occurs when immature white blood cells, produced in the bone marrow, keep multiplying. Different types of leukaemia originate from different cell types: lymphoid or myeloid cells. Therefore, leukaemia can be classified as lymphoid or myeloid, and as either acute or chronic. The majority (approximately 80%) of childhood leukaemias are acute lymphoblastic or lymphoid leukaemias (ALL). The remainder consists almost exclusively of acute myeloid leukaemia (AML). Chronic forms of childhood leukaemia are rare.[2]

The median age of childhood leukaemia patients is low overall, but shows a difference where the two types are concerned, ALL patients being younger (4 years, 9 months) than patients with AML (6 years, 1 month).[3] As the latency period can be several years, possible causes of childhood leukaemia may be

* Incidence: the frequency of new cases within a certain period.

found very early in childhood, in pregnancy, or even before conception. The same applies to possibly protective environmental influences.

Although improvements in treatment and care have led to a remarkable increase in survival rates in recent years, childhood leukaemias require burdensome and complication-prone treatments and remain lethal in a significant proportion of cases. In Western European countries the 5-year survival rate between 1988 and 1997 has been approximately 85% for ALL and less than 60% for AML.[4] Because of the young age of children with leukaemia, the mean number of disability related life years or years lost is relatively high compared to other cancers.

Trends in incidence and supposed role of the environment

Between 1978 and 1997 the age-standardised incidence rates for leukaemia in about twenty European countries have shown a slow but continuous rise from 4.0 to 4.5 per 100,000 children (age 0-14).[1,4,5] This increase can only partly be explained by changes in diagnostic methods and registration artefacts.[5] The patterns and magnitude of the increase therefore suggest that changes in lifestyle and in exposure to a variety of agents have contributed to the observed increase.[5]

A vast body of scientific literature on environmental factors that may be associated with the induction and development of childhood leukaemia is available, ranging from ionising radiation, electromagnetic fields and chemicals such as pesticides to infectious agents and lifestyle factors. In recent years several publications have discussed the incidence of childhood leukaemia around nuclear facilities in Germany and the observed associations with living near overhead power lines or with pesticide exposures.[6-9]

The specific dynamics of exposure in children can be expected to differ from that in adults. In addition to exposure during childhood, exposure of the mother during pregnancy and exposure of the parents before conception can also play a role. Furthermore, children are in general considered to be more sensitive to external influences, as a result of their developing physiology and behaviour. This sensitivity is especially high during the first weeks after conception, when parents might not even be aware of the pregnancy.

Gene-environment interactions

Exposure to environmental factors is, however, not the only cause. Gene mutations have been shown to play a central role in the aetiology of childhood leukaemia. Especially ALL, the most common type of cancer in children, is a heterogeneous disease in which different types of genetic abnormalities result in the development of multiple genetic subtypes (see 4.1). Genetic and environmental factors, and different types of environmental factors, may also be expected to interact. Different types of leukaemia may respond differently to

environmental factors. Moreover, some environmental influences may offer a measure of protection against childhood leukaemia. In exploring the role of environmental influences, these also need to be taken into account.

1.2 The Committee, its working procedures and objectives

Committee

The Chair of the SHC and the President of the HCN have established a multidisciplinary Committee to prepare an advisory report on the association between environmental factors and the incidence of childhood leukaemia. Its membership is listed in Annex A.

Working procedures

The Committee met eight times. During the review process several external experts were consulted (Annex B). Most of them were members of the HCN Standing Committees on Radiation and Health, on Health and the Environment, on Medicine and on Public Health, and members of the Reflection Groups Ionising Radiation and Non-Ionising Radiation and Chemical Agents of the SHC. A draft was also reviewed by members of EuSANH. The written comments have been discussed in a joint meeting with several reviewers. Finally the report has been validated by the Boards of the SHC and of the HCN.

Objectives

Given the rise in incidence and the possible association with environmental factors, the Committee's aim is to review the evidence, consider possible causal relationships and draw up recommendations for measures that could reduce the incidence of childhood leukaemia. To reach this aim, the Committee formulated the following objectives:

1 Collect epidemiological data from Belgium and the Netherlands on childhood leukaemia and discuss this in a European context.
2 Consider the evidence on genetic risk factors of childhood leukaemia.
3 Review the evidence on environmental factors regarding childhood leukaemia, discuss the relevance of indicators of environmental exposures and consider possible causal relationships with childhood leukaemia.
4 Propose measures to reduce the impact of environmental risk factors on childhood leukaemia, propose risk communication strategies, and advise on further research.

In dealing with the question of environmental factors, the Committee discusses physical, chemical and biological influences, excluding medication. Factors that

may be relevant as potential confounders* and effect modifiers**, such as genetic susceptibility, lifestyle factors and socio-economic status, are also taken into account. A review of diagnosis, treatment and survival rates of childhood leukaemia, however, is outside the scope of this advisory report.

1.3 Content of this report

In Chapter 2 the review methods are described. Chapter 3 is concerned with the first objective of the Committee: collecting and discussing the incidence data on childhood leukaemia in Belgium and the Netherlands within a European context. Chapter 4 deals with the relevance of genetic susceptibility. In Chapter 5, 6 and 7 the Committee reviews the evidence for causal relationships between the occurrence of childhood leukaemia and physical, chemical and other environmental exposures, thus addressing the third objective. Chapter 8 presents the overall conclusions of the Committee and the recommendations for risk management, risk communication and options for further research – the last objective of this advisory report.

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* Confounder: known risk factor for a disease associated with the exposure under study, which is not functioning as an intermediary factor in the causal relationship between exposure and effect (e.g. life style factors of socioeconomic status).[10]

** Effect modifier: factor that modifies the measure of effect of a causal factor under study (e.g. genetic susceptibility or age of exposure).[11]

2 Perspectives and review methods

2.1 A precautionary perspective

As will become clear from this report, knowledge about the impact of environmental and lifestyle factors on the occurrence of childhood leukaemia is, with a few exceptions, highly uncertain. In situations such as these, which are also characterised by complexity and ambiguity*, a precautionary perspective is recommended to guide the risk assessment and subsequent risk management.[12] Thus, the available scientific knowledge should be weighed with precaution in mind, sources of knowledge outside the area of science could be taken into account, and policy measures could be evaluated accordingly.

Benefits and costs always have to be balanced, but this is especially important when gaps in knowledge exist and possibly detrimental influences can be serious. Taking a precautionary perspective, measures could then be recommended of which the effect on the occurrence of childhood leukaemia is uncertain or thought to be limited, but that at least also will have other benefits.

2.2 Sources of scientific evidence

Scientific evidence for possible relationships between exposure to an environmental factor and childhood leukaemia is available from two sources: epidemiological and experimental data.

On the one hand, relevant evidence can be obtained from observational studies: epidemiological research in which the association between exposure to an environmental factor and the disease is explored. The three most important types of epidemiological studies are cohort studies, case-control studies and ecological studies**.

Epidemiological studies generally produce equivocal results, and for that reason the results are often insufficient to conclusively establish causal relationships.

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* Ambiguity relates to different value judgements and conflicting interpretations of the scientific knowledge and controversies about the factors that may cause the risks.

** In a *cohort study* a large group of initially healthy subjects is followed for long periods of time, varying from years to decades. Exposure to the factor of interest and the occurrence of disease is monitored, and in due time associations can be determined. This is usually a prospective type of study, which allows adequate exposure assessment. In a *case-control study* a group of patients with the disease of interest is selected, and for each case one or more control subjects is sought who do not suffer from the disease. A comparison between case-control pairs is then made regarding exposure

On the other hand, experimental data can be obtained in the laboratory by exposing human or animal cells (in vitro studies) or experimental animals (in vivo studies) to environmental factors. In some cases effects can be studied by exposing volunteers (human studies). In this way, knowledge can be gathered about mechanisms that might explain the associations observed in epidemiological studies or that indicate a possible role for a specific risk factor, even if relevant associations have not been observed or investigated.

In this report, the Committee uses four approaches to obtaining evidence for possible environmental influences on the incidence of childhood leukaemia.

Systematic reviews on childhood ALL and AML

The first line of enquiry has been to commission The Cochrane Childhood Cancer Group (CCG) in Amsterdam to prepare a systematic review of the available epidemiological evidence on the aetiology of childhood leukaemia. The literature retrieval followed a strict protocol with specific inclusion criteria, and items for study quality assessment were a priori defined in the study protocol.

Only publications evaluating 'environmental factors' were included that pertained to *childhood* leukaemia (i.e. that included subjects younger than 18 years at the time of diagnosis) and that presented data on ALL and/or AML separately. Because of the very large number of publications retrieved by the initial search, inclusion was limited to systematic reviews and meta-analyses with a systematic literature search published between 1990 and March 2010.

The year 1990 was chosen as a starting point since diagnostic methods to reliably differentiate between ALL and AML were not available before the 1980s, and pooling the data is not appropriate, given the different aetiology of the two types of leukaemia. The first eligible publications could therefore be expected to have appeared from 1990 onwards. One review per aetiological factor was selected: either the most recent one or the one with the largest search period.

The CCG has presented its findings in an 'Evidence Summary', which is published in conjunction with this report.[225] Summary tables derived from the CCG Evidence Summary are included in this report in Annex C. Conclusions from a systematic review of systematic reviews, such as the CCG Evidence Summary, are always based on an analysis of the primary data by the authors of

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to the factor of interest. This allows for conclusions on whether exposure is higher in the cases, which might be an indication of causality. One of the main problems with this type of study is that exposure has to be determined retrospectively, and often on the basis of recollection by the subjects. In an *ecological study* the occurrence of disease at the population level is investigated in relation to exposure to the factor of interest. A limitation of this type of study is the usually poor level of insight into trends and patterns of exposure at the population level, and the retrospective assessment of exposure. Another main problem is that information on confounding factors is generally missing or is available only at an aggregated level.

the original systematic reviews. However, if information on the primary data is not available, specific aspects, such as the quality of the included studies, cannot be discussed. Because of this limitation, and the wider scope of its objectives, the Committee also studied other evidence.

Systematic reviews on childhood leukaemia in general

Given the focus on systematic reviews and the required separate analysis of ALL and AML, the CCG Evidence Summary did not include several possibly important aetiological factors. From a clinical point of view this selection was warranted, but the Committee decided that additional information, specifically relevant for identifying the environmental factors associated with the aetiology of childhood leukaemia, should be weighed as well. It therefore systematically evaluated the data on childhood leukaemia in general, which were identified in the original CCG search for systematic reviews.

Ten systematic reviews were thus identified in the CCG search, in each of which 50% or more of the studies had been eliminated, as they only addressed childhood leukaemia in general. The results of the evaluation of these studies are presented in an 'Evidence Summary on Childhood Leukaemia in General', which is published alongside this report.[213] Summary tables derived from this Evidence Summary are included in Annex D.

Other epidemiological evidence

The CCG search focussed on systematic reviews that were published between 1990 and March 2010. As a consequence, systematic reviews published before 1990 were not included, and neither were narrative reviews. Moreover, dependent on their objectives, the systematic reviews did not review all earlier studies. Because important information from relevant studies could have been missed, the Committee identified key publications or reports from authoritative national or international expert panels, including results published before 1990 and reviews published since March 2010.

Experimental evidence

In order to assess causality, information on the mechanisms of leukaemogenesis also had to be taken into account. This means that in addition to epidemiological data, results from experimental studies needed to be considered.

The IARC*, an agency of the WHO, has evaluated several relevant risk factors and classified them according to their carcinogenicity. The Committee has taken into account the IARC Monographs in which these results are

* IARC: the International Agency for Research on Cancer of the World Health Organization (WHO).

presented. For some factors, such as ionising radiation, Committee members contributed additional experimental information.

In weighing the information, the Committee has considered that not all agents that have been shown to cause cancer in experimental animals can also be expected to cause cancer in humans, although the animal studies may strengthen the biological plausibility of an association.[13] Similarly, if an agent has been found to be carcinogenic in humans, this does not necessarily mean that it may cause (childhood) leukaemia.

2.3 Classifying evidence and possible causality

In evaluating the evidence for an aetiological role of environmental factors in the initiation or development of childhood leukaemia, the Committee considered two questions:

- What is the evidence for an association between the exposure to certain environmental factors and the incidence of childhood leukaemia?
- What is known about possible mechanisms that would explain an observed or hypothesised association between the exposure to certain environmental factors and the incidence of childhood leukaemia?

In answering the first question, the findings from epidemiological research play a central role. In answering the second question, evidence from experimental research is of primary importance.

To evaluate the strength of evidence for a causal relationship between an environmental factor and childhood leukaemia, the Committee has taken into account the well-established considerations put forward by Bradford Hill to interpret epidemiological studies: temporality, biological gradient (or exposure-response), consistency, strength, specificity, plausibility, coherence, experiment, analogy (see also Annex E).[14,15]

Evidence

The Committee has classified the epidemiological evidence for an association between the exposure to an environmental factor and the incidence of childhood leukaemia, using a modified version of the classifications by IARC and Wigle (see Annex F). The conclusions are presented on a three point-scale: [16,17]

- Sufficient (based on results from high-quality systematic reviews or other overwhelming evidence, e.g. high-quality large scale observational studies).
- Limited (based on results from low-quality systematic reviews or high-quality observational studies).
- Inadequate (based on results from low-quality observational studies or expert opinions).

Accordingly, the biological plausibility has been classified as high, moderate or low, as far as could be assessed from the available literature.

Possible causality

The Committee has classified its conclusions on a causal contribution of environmental exposures to the incidence of childhood leukaemia as:

- Established
- Likely
- Possible
- Uncertain
- Unknown.

These qualifications are based on the levels of epidemiological evidence and biological plausibility, as presented in the following table for the likelihood of causality:

Levels of scientific evidence		Epidemiological evidence for an association		
		Sufficient	Limited	Inadequate
Biological plausibility for a causal relation	High	Established	Likely	Possible
	Moderate	Likely	Possible	Uncertain
	Low	Possible	Uncertain	Unknown

In some classifications a fourth category of scientific evidence is added, to indicate whether there is sufficient evidence for the *absence* of (i.e. evidence against) an association or relation with a specific risk factor. In those situations a causal relation is classified as 'unlikely'. However, where environmental risk factors of childhood leukaemia are concerned this appeared seldom to be the case.

2.4 Presenting quantitative information on risks

When available, the Committee has presented quantitative information on the incidence of childhood leukaemia resulting from exposure to environmental factors in the form of the estimated fraction of childhood leukaemia cases that can be attributed to a given risk factor. This 'population attributable fraction' or PAF (sometimes called 'population attributable risk' or PAR) is expressed as a percentage.

Two types of information are needed to estimate the PAF:[18]

- The relative risk (RR): an estimate of the effect of exposure on the incidence of the disease.
- The prevalence (P) of exposure in the population.

The formula to calculate the PAF is:

PAF=[P*(RR-1)] / [1+P(RR-1)] * 100.

However, in most cases the information on exposure distribution required to perform this estimation is not available. The Committee has therefore attempted to provide expert calculations whenever it was possible to do so, in some cases using the exposure distribution of control groups as an estimate for the population as a whole. When applicable, this is stated explicitly.

2.5 Presenting recommendations

The Committee recommends measures that may contribute to the reduction of childhood leukaemia in the framework of precaution (see 2.1). The problem is complex and risk is created by a sequence of multifactorial elements. Causal evidence and plausibility range from 'unknown' to 'established', depending on the nature of contributing factors, while value judgements can differ.

How has the Committee arrived at these recommendations?

First, recommendations can be derived from available epidemiological evidence. Where this approach is applicable, the Committee has followed Wigle:[17]

- Where relationships between adverse health effects in children and environmental exposures are supported by *sufficient* evidence of causal relationships, there is a need for (a) policies and programs to minimise population exposures and (b) population-based biomonitoring to track exposure levels, through ongoing or periodic surveys with measurements of contaminant levels in blood, urine and other samples.
- For relationships supported by *limited* evidence, there is a need for targeted research and policy options ranging from ongoing evaluation of evidence to proactive actions.
- There is a great need for population-based, multidisciplinary and collaborative research on the many relationships supported by *inadequate* evidence, as these represent major knowledge gaps.

Which types of measures are appropriate depends on a large number of factors, including:

- The nature of the risk.
- The benefits of the activities associated with the risk.
- The availability of feasible measures or alternatives.
- The disadvantages (other risks and costs) of measures.

Finally, recommendations can be based on the quantitative contribution of a risk factor to the occurrence of a disease, expressed as the population attributable fraction (PAF) and defined as the proportional reduction that would occur if exposure were to be reduced to zero. Where formulating policies is concerned, this is the most important estimate.[19] Mostly, however, it is not possible to determine the PAF, due to a lack of data on the distribution of exposure in the target population.

3 Incidence of childhood leukaemia

In this chapter, the Committee presents epidemiological data on childhood leukaemia from Belgium and the Netherlands. In Belgium, childhood leukaemia is defined as acute leukaemia diagnosed before the age of fifteen, in the Netherlands before the age of eighteen. To allow a comparison, data from the Netherlands are also provided for the 0-14 years age group. Subsequently, the results are discussed in a European context. The chapter concludes with a paragraph on reported clusters of incidence.

3.1 Incidence in Belgium

In Belgium, the Belgian Cancer Registry (BCR) is responsible for data collecting. Data are available for all regions (Flanders, Wallonia and Brussels) from 2004 onwards.[20] For Flanders, population-based data are available from 1999. In Table 1 the childhood leukaemia incidence rates (WSR*) in Belgium are presented.

Table 1. Leukaemia in children (0-14 years) in Belgium (2004-2008): absolute numbers over the 5-year period and standardised incidence rates (WSR) by diagnosis.

ICCC[a] category	Absolute numbers (total male and female)	Incidence rate (number/ 100,000 person-years; total male and female)	Percentage of total
Ia Acute lymphoid leukaemias	333	3.95	79
Ib Acute myeloid leukaemias	61	0.71	15
Ic Chronic myelopro-liferative diseases	6	0.06	<1
Id Myelodysplastic syndromes and other myeloproliferative diseases	18	0.21	4
Ie Unspecified and other leukaemias	2	0.02	<1
Total	420	4.94	100

[a] International Classification of Childhood Cancer.[21]

* WSR (World Standardised incidence Rate): weighted average of the individual age-specific rates using the World Standard Population for standardisation, expressed as the number of new cases per 100,000 person-years.

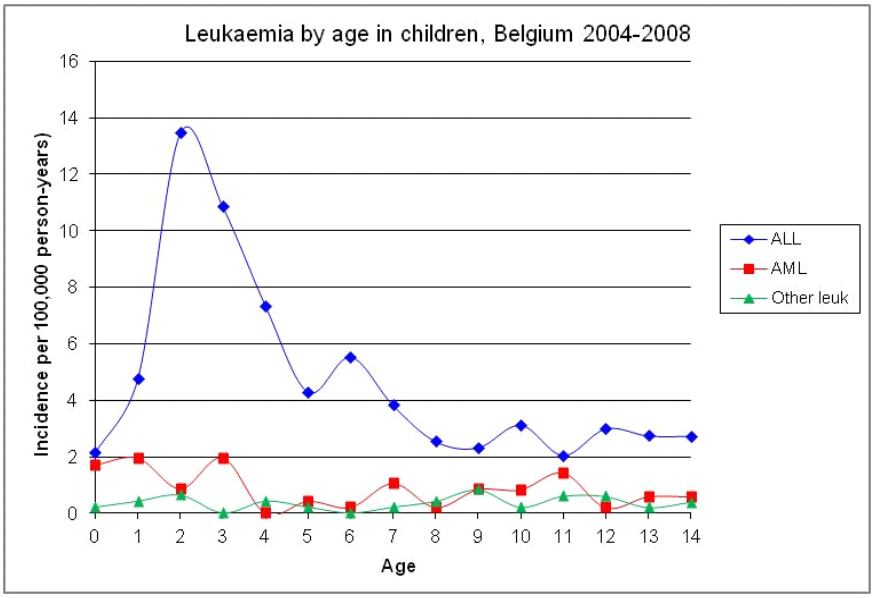

Figure 1. Age-specific incidence rates of leukaemia in children (0-14 years) in Belgium (2004-2008).

For the period 2004-2008, 23% of all childhood cancers were leukaemias. The average number of new cases per year was 67 for ALL and 12 for AML. The standardised incidence rate (WSR) was 3.95 per 100,000 person-years for ALL and 0.71 for AML. In Figure 1 the childhood leukaemia age-specific incidence rates in Belgium are presented.

As complete data collection in all regions only started in 2004 and only small numbers of cases are involved, the data have a large variability. In Flanders, incidence rates of childhood leukaemia are available from 1999 onwards. The yearly incidence (WSR) for ALL and AML in Flanders between 1999 and 2008 is presented in Figure 2.

For the period 1999-2008 the estimated annual percentage of change (EAPC) showed a non-significant decrease: -2.57% for ALL (p=0.23) and -5.01% for AML (p= 0.44).

3.2 Incidence in the Netherlands

In the Netherlands, the Dutch Childhood Oncology Group (DCOG) is responsible for collecting data on childhood cancers diagnosed up to 18 years of age. Data are available from all seven childhood oncology centres, starting in 1972.[20,22] Since 1984, data are available per type of leukaemia (ALL/AML).

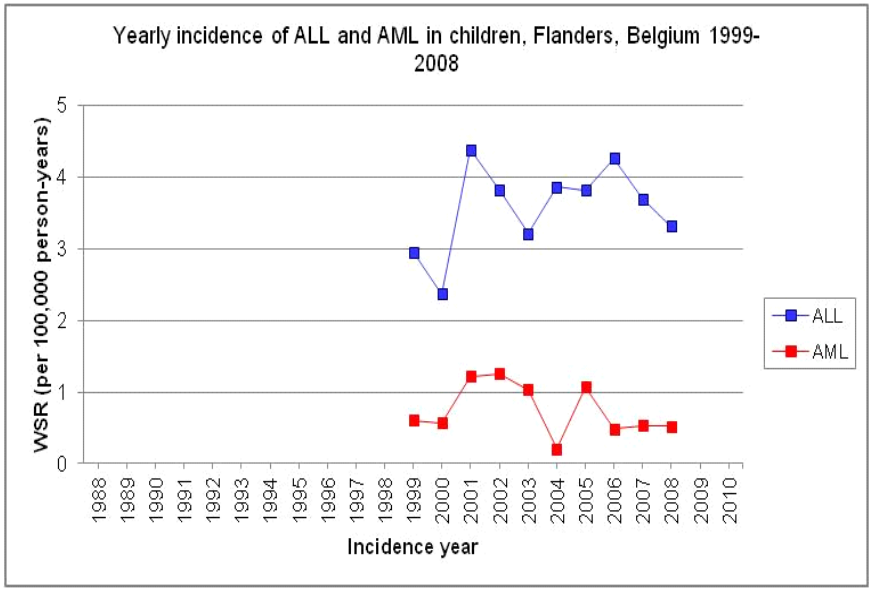

Figure 2. Yearly incidence (WSR) of ALL and AML in children (0-14 years) in Flanders (1999-2008).

In Table 2 the childhood leukaemia incidence (WSR) in the Netherlands is presented.

Table 2. Leukaemia in children (0-14 years) in the Netherlands (2004-2008): absolute numbers over the 5-year period and standardised incidence rates (WSR) by diagnosis.

ICCC[a] category	Absolute numbers (total male and female)	Incidence rate (number / 100,000 person-years; total male and female)	Percentage of total
Ia Acute lymphoid leukaemias	537	3.77	75
Ib Acute myeloid leukaemias	115	0.81	16
Ic Chronic myelopro-liferative diseases	12	0.07	2
Id Myelodysplastic syndromes and other myeloproliferative diseases	47	0.35	7
Ie Unspecified and other leukaemias	4	0.04	<1
Total	715	5.04	100

[a] International Classification of Childhood Cancer.[21]

For 2004-2008 the average number of new cases per year was 108 for ALL and 23 for AML. The standardised incidence rate (WSR) per 100,000 person-years was 3.77 for ALL and 0.81 for AML.

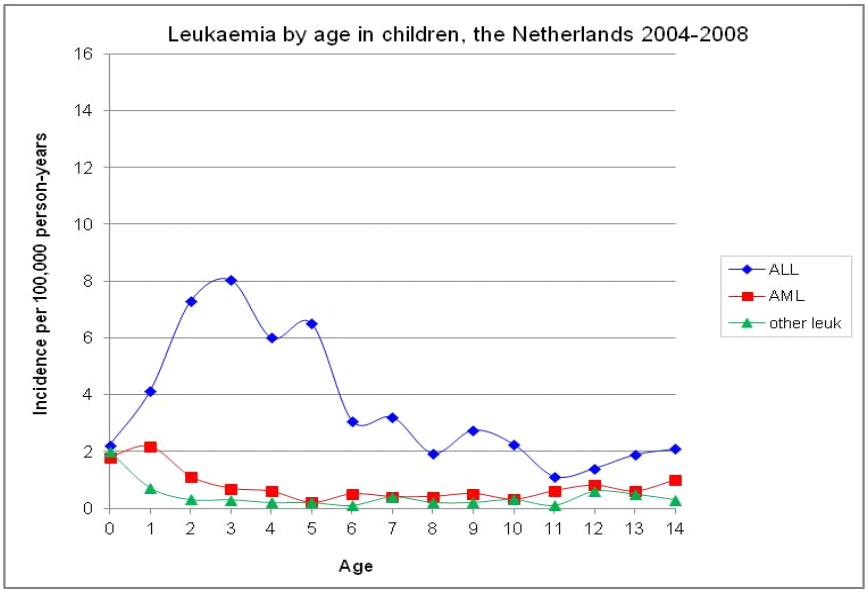

Figure 3. Age-specific incidence rates of leukaemia in children (0-14 years) in the Netherlands (2004-2008).

In the case of ALL, 45% of the children is diagnosed at 1-4 years of age, 33% at 5-9 years of age, 15% at 10-14 years of age (Figure 3).[23] Another 7% are diagnosed at 15-17 years of age. The latter group is sampled 'registry based' instead of 'population based', and is therefore not presented here. 'Registry based' means that children are only included in the DCOG registry if they are treated in a paediatric oncology centre. Children aged 15-17 are sometimes referred to a haematologist for adults.

In Figure 4 the incidence (WSR) of ALL and AML in the Netherlands between 1988 and 2010 is presented.

Over the whole period, 1988-2010, the estimated annual percentage of change (EAPC) has not been statistically significant: 0.57% for ALL (p=0.10) and -0.45% for AML (p= 0.44). However, broken down per decade, the incidence of ALL shows a statistically significant increase of 2.5% (p=0.003) from 1990 to 2000, and a non-significant decrease of -1.9% (p=0.07) from 2000 to 2010. The incidence of AML shows a non-significant decrease of -1.9% (p=0.17) from 1990 to 2000, and a non-significant decrease of -1.5% (p=0.52) from 2000 to 2010. According to the DCOG registry, the increase of ALL in the nineties cannot be explained by registration artefacts, since the registry has already started in the seventies and has not been changed since the eighties.[23]

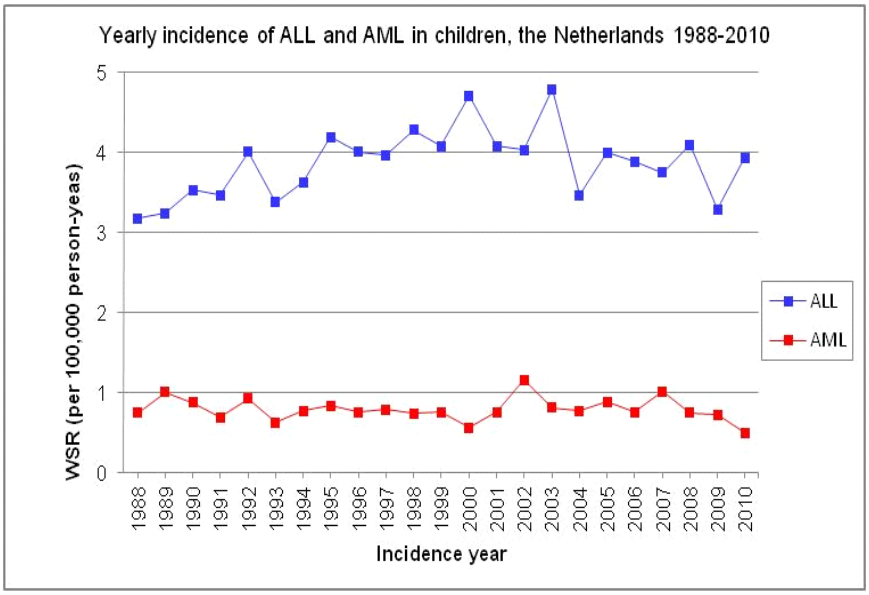

Figure 4. Yearly incidence (WSR) of ALL and AML in children (0-14 years) in the Netherlands (1988-2010).

3.3 Incidence in Europe

The standardised incidence rates (WSR) per 100,000 person-years for all childhood leukaemias combined over the period 2004-2008 are comparable for Belgium and the Netherlands (see Table 3). They are also approximately similar to the incidence rates in France over the period 2000-2004, to those in Sweden over the period 1990-1998 and to those in Europe as a whole over the period 1993-1997. However, as this comparison is based on incidence rates over different time periods, caution in drawing conclusions is required.

Table 3. Age-standardised incidence rates (WSR) per 100,000 person-years of childhood leukaemia in different countries.

	Belgium 2004-08	The Netherlands 2004-08	France 2000-04[24]	Sweden 1990-98[25]	Europe 1993-97[4]
ALL	3.95	3.77	3.42	4.01	3.72
AML	0.71	0.81	0.72	0.49	0.65
All types	4.94	5.04	4.59	5.10	4.45

The incidence of childhood leukaemia in general ('all types') is statistically higher in Northern Europe (Scandinavia: 4.8 per 100,000 person-years, aged 0-14) and statistically lower in eastern Europe (3.9 per 100,000 person-years, aged 0-14) than the incidence determined for Europe as a whole.[1]

During the last two decades of the past century the incidence of childhood leukaemia in Europe has shown an increase. This particularly applies to ALL, where a rise of 0.8% per year was seen in children (age 0-14 years: $p<0.0001$), and a rise of 1.9% per year occurred among adolescents (age 15-19 years: $p=0.008$).[4] This increase can only partly be explained by changes in diagnostic methods and registration artefacts.[5]

It is currently unclear whether the increase in leukaemia incidence has continued in recent years. Data from the Netherlands and Belgium suggest no further increase since the year 2000. An update on the time trend of leukaemia incidence in Europe by the ACCIS* project, which is expected to be available by the end of 2012, may be able to confirm this.

3.4 Reported clusters and statistical clustering of incidence

When dealing with the incidence of childhood leukaemia, one other topic needs to be addressed. There are many reports about 'clusters': unusually high numbers of cases in a given area, period or population.[26] Statistically significant excess occurrences of leukaemia have been reported in a large variety of situations, for example: in a horticultural community in the Netherlands,[27] near nuclear power plants in Germany and the UK,[7,28] in areas around military encampments in England and Wales,[29] in villages with wartime evacuation refugees in England and Wales,[30] in rural areas with a high proportion of oil industrial workers in Scotland,[31] near large rural construction sites (coal fired or hydropower stations and refineries) in Great Britain,[32] in the neighbourhood of a navy base in the US,[33] and near a coke by-products plant of a steel factory in Australia.[34]

Some of these clusters will have occurred by chance: children with leukaemia who happen to live in close proximity. In other cases, however, a statistical variation should be considered very unlikely, since the difference between the number of observed and expected cases is too large to be attributed to chance alone. Different mechanisms have been proposed to explain these occurrences.

The British Committee on Medical Aspects of Radiation in the Environment (COMARE) has studied the question as to whether or not childhood cancers have a 'natural' tendency to aggregate or 'cluster' closer in space or time than one would expect by chance alone.[35] It appeared that the incidence of childhood leukaemia in Great Britain (1969-1993) occurred in a non-random pattern, varying more than would be expected if it were due to chance variations. These results are consistent with the hypothesis that a non-random distribution of leukaemia cases could be associated with the geographical distribution of environmental risk factors. In the British study, however, it could not be established what these factors were.

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* ACCIS: Automated Childhood Cancer Information System.

The modest evidence for time-space clustering is compatible with the 'population-mixing' hypothesis of Kinlen and the 'delayed-infection' hypothesis of Greaves.[36] Both hypotheses posit that childhood leukaemia is a rare response to one or more common infections acquired by personal contact under particular 'modern' socio-demographic circumstances (see Chapter 7).

3.5 Conclusion

The incidence of ALL in Europe has slowly but continuously increased during the last two decades of the 20th century. This increase can only partly be explained by improvements in diagnostic methods and registration.

In the Netherlands, a statistically significant increase of ALL has been seen during the last decade of the past century. Since the year 2000, however, this increase seems to have come to a halt, and has possibly been reversed. The same seems to apply to Belgium. The incidence of AML has remained relatively stable.

In the UK, it has been demonstrated that the geographical incidence of childhood leukaemia shows more clustering than would be expected if it were due to chance variations. This finding is consistent with the hypothesis that a non-random distribution of cases of leukaemia (i.e. clustering) could be due to the geographical distribution of environmental risk factors, including infectious agents.

4 Genetic factors

Although the focus of this report is on environmental risk factors for the induction and development of childhood leukaemia, the Committee briefly considers the role of genetics, primarily to demonstrate the complexity of the issue. Given this limited objective, a systematic search of the literature has not been undertaken, and an extensive review of the scientific data is not provided. First, the different genetic subtypes of childhood leukaemias will be described. Then two types of genetic susceptibility will be discussed.

4.1 Genetic subtypes

ALL and AML have distinct origins. They involve malignant transformation of lymphoid and myeloid progenitor cells*, respectively.[2] Furthermore, for AML (~15% of cases) as well as for ALL of B-cell lineage (~70-75%) and T-cell lineage (~10-15%)**, many different subtypes can be distinguished, each characterised by specific genetic abnormalities.[37] In Figure 5 the variation in age-specific incidence of different genetic subtypes of childhood leukaemia in the Netherlands is presented, starting in 1997.[23]

In the cord blood of healthy newborns the prevalence of a TEL/AML translocation (a preleukaemic lesion in circa 1:4 of ALL patients) is circa 1 in 100, while only 1 in 10,000 will later in life develop ALL with TEL/AML.[38,39] This forms an argument for a multistep pathogenesis: since at least 99% of the children with this 'first hit' will not develop leukaemia, there are more hits necessary to develop leukaemia. A recent international study revealed within families a high concordance of specific subtypes of childhood ALL, such as high-hyperdiploidy, indicating strong genetic or environmental risk factors for childhood ALL.[40]

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* A progenitor cell is a cell that, like a stem cell, has a tendency to differentiate into a specific type of cell, but is already more specific than a stem cell and is pushed to differentiate into its 'target' cell. The most important difference between stem cells and progenitor cells is that stem cells can replicate indefinitely, whereas progenitor cells can only divide a limited number of times.

** B-cells are lymphocytes produced in the bone marrow. The precursors of T-cells are also produced in the bone marrow, but they leave the bone marrow and mature in the thymus.

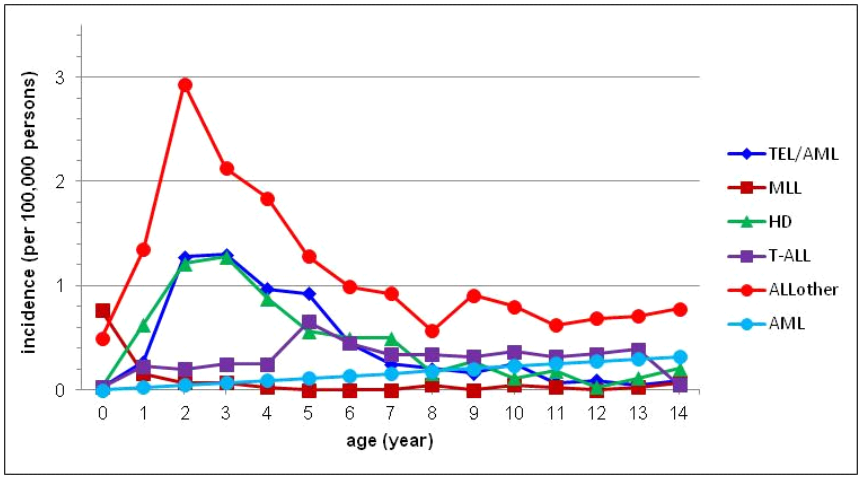

Figure 5. Age-specific incidence of childhood leukaemia by genetic and phenotypic subtype in the Netherlands (1997-2010). TEL/AML: B-cell Acute Lymphocytic Leukaemia (ALL) with TEL/AML fusion; HD: B-cell ALL with high hyperdiploidy (>50 chromosomes per cell); MLL: B-cell ALL with abnormalities including the mixed lineage leukaemia gene; T-ALL: T-cell ALL; ALLother: all other ALL; AML: Acute Myelocytic Leukaemia.

4.2 Genetic susceptibility

Different genetic abnormalities are at the origin of the different types of leukaemia. Childhood ALL is a multifactorial malignancy with age-specific deletions, insertions and chromosomal translocations.[41] Genetic factors might influence the risk induced by environmental factors.[42]

The aetiology of acute leukaemia in children is characterised by immature blood cells acquiring different consecutive genetic abnormalities. A susceptibility to these abnormalities occurring can be inherited. However, most abnormalities are acquired gene mutations in the genetic material of somatic (blood precursor) cells.

4.2.1 Inherited genetic susceptibility

Evidence

Strong evidence for a genetic susceptibility to childhood leukaemia is provided by the increased risk associated with particular genetic disorders, such as Down's syndrome (trisomy 21).[43] However, even in the absence of these predisposing conditions, a genetic susceptibility may contribute to the origin of childhood leukaemia. This genetic susceptibility is related to so-called genetic

polymorphisms*.[44]

Until recently, studies looking for polymorphisms related to the risk of leukaemia generally used a 'candidate gene'** approach in a case-control design. These candidate gene studies were evaluated in a systematic review and meta-analysis.[45] The authors identified significant associations between childhood ALL and eight polymorphisms.

They mention, however, that numerous studies showed a defective methodological design and that their findings should be interpreted with caution, since the estimated 'false-positive reporting probabilities' for each association were considerable. Notably, none of the eight associations described in this meta-analysis were identified in the 'genome wide association studies' by Papaemmanuil et al.[46] Although some methodological issues might explain this discrepancy, it more likely underscores the proneness of identifying false positive associations in previous studies. Also, the genes studied in the candidate gene studies were often selected for practical reasons, because data were available from other studies, such as the relation between polymorphism and the toxicity of chemotherapy.

With the development of high throughput genotyping techniques, genome-wide association studies have become a feasible objective. In two landmark studies, using different genotyping platforms, strong susceptibility loci were identified.[46,47] Genetic variation at these loci not only was associated with the development of ALL, but also with specific subtypes of ALL. The initially reported associations were verified in a replication study in precursor B-cell ALL, the most frequent type of ALL.[48]

Although association studies might provide some mechanistic insights into the development of childhood leukaemia, the contribution of the described polymorphisms to leukaemic transformation remains unclear. Nonetheless, some studies convincingly have identified predisposing loci.[49] However, modulation of the risk by environmental factors remains unexplored.

Public health relevance

Less than five per cent of childhood cancers reflect well-known hereditary cancer disposition syndromes.[50] This means that more than 95% of children develop acute leukaemia in the absence of a predisposing syndrome.

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* Polymorphisms: variations in genes.

** Candidate gene: gene with a biologically plausible function in the development of a specific disease.

4.2.2 *Acquired genetic susceptibility*

Evidence

In general, DNA abnormalities (gene mutations) play a major role in carcinogenesis.[51] The vast majority of mutations in human tissues arise spontaneously and are due to endogenous factors. Only a small fraction of these acquired mutations, however, convert a normal cell into a cell that is initiated towards the development of cancer.[52]

It is assumed that in most instances the initiation event is due to a mutation that may, for instance, cause inactivation or loss of a gene involved in the repair of damaged DNA. Another mechanism that may be involved in carcinogenesis is modification of gene expression by receptor binding or DNA methylation by specific chemicals. The regulation of gene expression by DNA methylation is a so-called epigenetic mechanism, for instance expressed as an enhanced proliferation of embryonal blood cells. The aetiology of leukaemia in children, especially ALL, is characterised by immature blood cells acquiring different consecutive genetic abnormalities, the first ones often occurring before birth.[36,53] However, only few children who are born with a chromosomal translocation will develop ALL, proving that these are preleukaemic changes and that leukaemogenesis is multifactorial and depending on multiple consecutive events. The 'first hit', most likely acquired during pregnancy, will give rise to preleukaemic cells and clones being more susceptible to additional oncogenic events, the 'second hit'. Most children with ALL carry 6 up to ~20 different genetic abnormalities in their leukaemia cells; in AML the number of genetic abnormalities is lower.[54,55] The genes involved often play a role in the differentiation or proliferation of blood cells.

Although the causes of the oncogenic events remain largely unknown, the acquired genetic susceptibility is especially high during the first weeks of pregnancy, when parents might not even be aware of the pregnancy. This mechanism shows similarities with mechanisms in the development of congenital abnormalities, miscarriages, premature birth, intrauterine growth delay or other adverse pregnancy outcomes, since these are all related to cellular damage in the early development of the child. Depending on the phase of pregnancy in which the foetus is exposed to toxic agents, different outcomes may occur:

- Death of the embryo during the pre-implantation phase (first week).
- Malformations due to disturbed organ development (first trimester).
- Mental retardation due to disturbed development of the brain (first and second trimester).
- Increased risk of (childhood) cancer.

Public health relevance

Genetic susceptibility factors, either separately or in conjunction with environmental factors, may be involved in the majority of childhood leukaemias that cannot be explained by identified specific genetic and environmental risk factors.[56] In that respect, their relevance for public health is much greater than that of inherited genetic susceptibility.

4.3 Conclusion

Genetic polymorphisms might result in an increased vulnerability and therefore in a higher risk of developing childhood leukaemia. Most cases of childhood leukaemia result from a combination of (prenatal) initiation through the occurrence of genetic abnormalities and postnatal acquisition of multiple genetic abnormalities in haematopoietic progenitor cells.

Although the identification of genetic abnormalities has led to groundbreaking insights into the disrupted cellular pathways in leukaemic transformation, their origin is as yet unclear. However, insight into the genetic susceptibility of childhood leukaemia to risk factors is emerging, although the interaction with environmental factors is still largely unknown.

5 Physical environmental factors

In this chapter the role of physical environmental influences on the induction and development of childhood leukaemia is discussed. The Committee evaluates the evidence on ionising radiation, extremely low-frequency magnetic fields, radiofrequency radiation and diagnostic ultrasound scans during pregnancy.

5.1 Ionising radiation

5.1.1 Introduction

To evaluate the possible effect of ionising radiation on the incidence of childhood leukaemia, the Committee first discusses the evidence regarding ionising radiation in general. Since the exposure situations can show great variation, this is followed by a more specific evaluation, in which the Committee discusses five types of exposure, and assesses their possible contribution to the incidence of leukaemia in Belgium and the Netherlands:

- Natural radiation exposures.
- Medical radiation applications.
- Parental occupational radiation exposure.
- Residential proximity to nuclear facilities.
- Radiation accidents.

These exposure situations have been selected either because they are relevant in terms of their contribution to the exposure of the Belgian and Dutch population to ionising radiation, or because of their relevance in policy and societal debates.[57,58]

Types of ionising radiation

Ionising radiation is the scientific term for the phenomenon colloquially referred to as radioactive radiation or often, in short, as radiation. The term, however, covers various types of high-energy electromagnetic radiation and high-energy particles of subatomic dimensions. Examples of the former are X-rays generated by radiation machines and gamma rays emitted by radioactive substances. Examples of the latter are beta rays – electrons emitted by radioactive substances – and electron beams generated in so-called accelerators. Some radioactive substances emit positive electrons or positrons which also fall in the category of

ionising subatomic radiation; an important use of such substances is in positron emission tomography (PET scan). Other particle-type ionising radiations are alpha radiation – helium nuclei emitted by radioactive, heavy nuclei, e.g. radon – and neutrons released in nuclear fission or generated in particle accelerators.

Ionising radiation is applied in medicine for diagnostic and therapeutic purposes, in industrial radiography, in various forms of scientific research and in the production of electricity through nuclear energy. The radiation can be a by-product, as with the release of radioactive substances into the environment by nuclear energy installations, but it also occurs naturally. As a result, all humans are exposed to cosmic radiation. When living at high altitudes and in aviation this type of exposure is increased. Furthermore, some radioactive substances are a natural part of the biosphere. Human exposure to these natural forms of radiation, however, depends on location and behaviour. Stony materials, for instance, have a much higher concentration of natural radioactivity than wood. The exposure to ionising radiation from natural radioactive substances is therefore quite variable.

5.1.2 Ionising radiation in general

Radiation dose

Ionising radiation manifests itself in a great variety of forms. Not all types of radiation and radiation energy have been studied in detail, neither epidemiologically nor in the laboratory, either in relation to cancer in general or leukaemia in particular. However, the general scientific view is that what holds for one type of radiation also holds for another, at least in a qualitative sense.[59]

Central in this view is the absorption of radiation energy resulting in ionisation events that directly or indirectly affect biologically sensitive molecules, in particular DNA. Radiation exposure can be quantified in terms of an 'equivalent dose'*, using sievert (Sv) as a unit. It is generally assumed that the risk of radiation exposure with DNA as a target is proportional to the absorbed energy, i.e. the equivalent dose. However, recent research has indicated that other mechanisms that do not directly affect DNA may cause harm as well.[61] Whether these effects are proportional to the equivalent dose is as yet uncertain.

In describing the exposures of populations, the quantity 'effective dose' is commonly used.** In the case of a (more or less) uniform exposure of the body, the effective dose is equal to the whole body equivalent dose. In the case of non-uniform exposure, for instance after ingesting radioactive substances, the

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* Equivalent dose: the quantity of radiation energy absorbed at a certain point in the body per unit mass, adjusted for the biological effectiveness of that specific form of radiation.[60] 1 sievert (Sv) corresponds to 1 $J \cdot kg^{-1}$.

** Effective dose: a whole body equivalent dose corrected for differences in radiosensitivity related to cancer induction between the various organs and tissue.[60]

effective dose is taken to represent a similar cancer risk as in the case of uniform exposure.

For leukaemia, the exposure of the lymphatic system, and in particular the red bone marrow, is assumed to be especially relevant. The exposure quantity is therefore usually established to be the equivalent dose to the red bone marrow. For external exposures to ionising radiation, e.g. from cosmic rays or gamma rays from natural radioactivity in soil and building materials, this quantity can be equated to the exposure of the whole body. However, after the inhalation or ingestion of radioactive substances the exposure of the body is not uniform. In that case, the bone marrow equivalent dose has to be derived from complex calculations, taking into account the distribution and fate of the radioactive substances in the body.[62-68] The available information on the relation between exposure to ionising radiation and leukaemia includes the exposure of embryo and foetus after the intake of radioactive substances by the pregnant mother, and the doses from ingestion of radioactive substances with mothers' milk. The Committee, however, stresses that such data should not be used uncritically, since the calculations are based on biokinetic models that might change as more becomes known about the way substances are transported through the body, and how they are transformed and retained in the various organs. An example is the model used to calculate the exposures from noble gases. It uses irradiation of the skin or of the whole body (depending on the radiations emitted), but does not take into account inhalation and absorption in the lungs, nor the solubility in body fat.

Another reservation is in order. Even though the equivalent dose concept is commonly used to estimate radiation risk and to derive standards for radiation protection purposes, some doubt exists as to whether this concept is fully applicable in the exposure regimes generally encountered in the environment, in the work place and through medical diagnostic procedures. Given the present insights in radiation disease mechanisms, however, it has so far not been possible to propose a new or adjusted concept.

Epidemiological evidence

X-rays and radioactive substances were discovered at the end of the 19th century. Not long afterwards, indications of negative health impacts became apparent.[69] 'Radiation workers' lost part of their hair and complained about burned skin and vomiting.[70] In the first decades of the 20th century, cases of cancer were observed and related to the, often high, radiation exposure of radiation workers. A first report of leukaemia after prolonged exposure to radiation is dated 1911.[70]

In the course of the years, evidence has been gathered about the negative health impacts of ionising radiation at much lower exposure levels. Pertinent information about the health risks of ionising radiation exposure was obtained from studies among the survivors of the atomic bomb explosions above the

Japanese cities of Hiroshima and Nagasaki at the end of World War II.[71] Also, follow up studies of populations that were irradiated for medical purposes and of occupationally exposed populations have provided information about radiation risks. From these research data, and the evaluations by international and national scientific committees, evidence has emerged on the relationship between ionising radiation exposure and the incidence of childhood leukaemia. The Committee will use this information as a basis for its conclusions.

It is not scientifically disputed that ionising radiation exposure may cause leukaemia. An exception is the occurrence of (adult) chronic lymphatic leukaemia where radiation does not appear to play a role.[72] The Biological Effects of Ionising Radiation Committee (BEIR) of the US National Academy of Sciences has established relationships between radiation exposure and the incidence of leukaemia in the US population as a function of the age when exposure occurred and the time lapsed since the exposure, using the atomic bomb survivor data in Japan as a basis.[73] The so-called latent period, between the time of exposure and the time of increased leukaemia risk, lasts a few years. After a further period of five years, the risk tends to decrease.

The age at which exposure occurs appears to be relevant: the lower the age at the time of exposure, the higher the lifetime risk.[74] Furthermore, after prenatal medical exposure through irradiation of the mother and medical exposure of young children, increased risks of childhood leukaemia have been observed.[59,70,72,75,76]

Other evidence

Experimental studies, i.e. laboratory research with cell lines and experimental animals, have provided insight in the mechanisms that operate on the pathway from exposure to disease. From the evidence gathered, it has become clear that exposure to ionising radiation has the potential to, directly or indirectly, affect the genetic information (DNA) in the nuclei of the cells in the body, which may lead – sometimes after many years – to cancer, including leukaemia.

Damage to germ cells may lead to hereditary diseases, while in utero irradiation can cause congenital malformations and other damage.[59] Whether direct or indirect processes at a cellular level, or both, affect the genetic properties of cells, is at present a matter of discussion.[77,78] The foetus and the infant may be particularly vulnerable, given the relatively rapid division and multiplication of cells in the growing organism.

An important issue is whether exposures to ionising radiation at the low levels and rates encountered normally in the environment and in the work place may also lead to an increased risk of cancer, hereditary effects or other disease.[78,79] Mainly based on experimental studies, international review committees have opted, in any case with respect to cancer induction, for the absence of an

exposure threshold below which the risk would be nil.[60,78] The Committee feels that, with respect to radiological protection measures and policies, this interpretation of the available evidence is a prudent option. It will therefore follow this approach in its discussion of the relation between the risk of childhood leukaemia and exposure to ionising radiation.

The precise nature of the relationship between low level exposures and health effects, in particular the risk that cancer will occur, is, however, not well known*.[80] Based on insights in the processes leading to cancer, a linear relationship between radiation exposure quantities and cancer risk is widely assumed.[60,79] However, there are indications that this relationship may in some situations underestimate the risk associated with radiation.[81] Furthermore, research into the inter- and intracellular processes challenges the linear non-threshold model for cancer induction, and raises the possibility of protective responses at relatively low exposure (below 100 mSv).[82]

However, the newer findings so far have only added complexity, suggesting both overestimation and underestimation of the risks at low doses, making it difficult to propose a better model.[80]

Evaluation

Following the UNSCEAR** and other international review committees, the Committee regards the findings from epidemiological research and research into the mechanisms of cancer inductions as evidence for the claim that exposure to ionising radiation of the foetus and of young children can cause childhood leukaemia. The Committee denotes the level of evidence for a causal relationship between exposure to ionising radiation and childhood leukaemia from both epidemiological research and laboratory research as **established**.[59,72,75]

5.1.3 Natural radiation exposures

The exposure (average effective dose) to natural ionising radiation from cosmic origin, from radioactive substances in soil and building materials, and from natural radioactive substances in the body (not including the contribution from inhaled radon decay products) is about 1 millisievert (mSv) per person per year both in Belgium and in the Netherlands.[58] This exposure is quite uniformly distributed over the body and therefore the bone marrow equivalent dose (relevant for leukaemia) is equal to the effective dose. In the Netherlands, people are rather uniformly exposed throughout the country. In Belgium, exposures in

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* The data of the Japanese atomic bomb survivors suggest a linear-quadratic exposure-response relationship for leukaemia[74]. However, for the exposures commonly encountered in the present day environment or at work a linear relationship, extrapolated downwards from the epidemiological data, is also not inconsistent with the data.

** UNSCEAR: United Nations Scientific Committee on the Effects of Atomic Radiation.

the South are higher than in the North, due to higher concentrations of radioactivity in the soil.[57] The maximum difference is about 0.6 mSv per person per year. A population group receiving relatively high exposures to cosmic radiation is aircraft personnel (see 5.1.5).

Decay products of the noble gas radon are radioactive forms of polonium, bismuth and lead*. Radon is released by soil and stony building materials. The decay products get attached to airborne dust particles. When inhaled, they may be deposited in the lungs, and after absorption they may irradiate other organs. Due to radon accumulation in dwellings, exposure is considerably higher indoors than outdoors, and will depend on ventilation (replacement of indoor air by outdoor air), the degree to which radon from the basement or crawl space may diffuse into the living quarters and the choice of building materials.

Radon concentrations in dwellings in the Netherlands amount on average to 30 $Bq \cdot m^{-3}$ **, with building materials as the main contributor (about 70%).[85] The variation from dwelling to dwelling is relatively small from an international perspective; concentrations above 100 $Bq \cdot m^{-3}$ are quite exceptional.

In Belgium, the situation is different. The average concentration in dwellings is about 50 $Bq \cdot m^{-3}$, whereas in the South concentrations above 400 $Bq \cdot m^{-3}$ are found in a substantial fraction of the dwellings.[57,86] The contribution from the soil below a dwelling is much more important in Belgium than in the Netherlands.

However, the contribution of the inhalation of radon and radon decay products to bone marrow dose is quite uncertain. Estimates of bone marrow equivalent doses vary from 0.1 to 1 mSv per year at an exposure concentration of 200 $Bq \cdot m^{-3}$.[87] This means that for the average radon concentrations, the bone marrow equivalent dose may vary in the Netherlands from 0.015-0.15 mSv, and in Belgium from 0.025-0.25 mSv.

Epidemiological evidence

Except in the case of radon exposures, the Committee is not aware of research that has specifically investigated the relationship between natural background radiation and childhood leukaemia. Several studies did compare leukaemia incidence or mortality in areas with different natural radiation exposure due to differences in radioactivity in the soil.[59] Even though some studies included quite large populations (several tens of thousand), generally no statistically significant differences were found between the 'high' and 'low' exposure regions. However, other genetic and environmental factors may have played a role that could not be accounted for.

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* Two radioactive forms of radon exist that are denoted somewhat confusingly as 'radon' and 'thoron'. In view of possible health effects – mainly lung cancer – 'radon' is of primary importance, although in the Netherlands recently the contribution of 'thoron' has also been investigated.[83,84]

** The unit of radioactivity is becquerel (Bq). 1 Bq equals one disintegration per second.

Regarding the exposure to radon decay products, a recent review has summarised data from ecological and case-control studies on the association with childhood leukaemia.[88] By applying a meta-analysis, a statistically significant increased risk for indoor radon exposure was noted for ALL and for childhood leukaemia in general. However, the authors concluded that more evidence is required to confirm this association.

Evaluation

The Committee concludes that the epidemiological evidence for an association between environmental radon exposure and childhood leukaemia is *limited*. It is, however, consistent with an assumed causal relationship with naturally occurring ionising radiation exposure.

Public health relevance

For Great Britain, the contribution of natural radiation exposure to the incidence of childhood leukaemia has been estimated at 15-20%.[89-91] This estimate is based on risk data derived from the studies on Japanese atomic bomb survivors, and various models.[72,73,92] It should, however, only be used as an indication. Recently, a large case-control study in Great Britain supported the extrapolation of high-dose rate risk models to protracted exposures at natural background exposure levels.[93] There appeared to be 12% excess relative risk of childhood leukaemia per mSv of cumulative red bone marrow dose from gamma radiation, insensitive to adjustment for socio-economic status.

Given the similarity of exposure in Great Britain to that in Belgium and the Netherlands, the Committee assumes that similar calculations for Belgium and the Netherlands would lead to an estimate of the same magnitude.

Recommendations

In seeking policy measures to protect against natural radiation exposure with the aim to reduce lung cancer, the focus has mainly been on building construction (subsoil and crawl space ventilation) and the choice of building materials. In this way, exposure to radon and its decay products originating from soil and building materials may be reduced. Especially in dwellings in the south of Belgium, the radon concentrations are relatively high. Knowing this, the Belgian authorities have been providing information on measures that may help reduce this exposure.[86] In the north of Belgium and in the Netherlands, the possibilities for exposure reduction are more limited, although some decrease may still be possible by using building materials with low radium and thorium content, and by providing adequate ventilation.[94]

Where radon is concerned, the main public health argument for taking measures is its impact on the occurrence of lung cancer. However, a reduction in exposure may also contribute to a decrease in the incidence of childhood leukaemia, but this would be expected to be limited.

5.1.4 *Medical radiation applications*

Medical applications of ionising radiation encompass diagnostic investigation and therapeutic treatment. The main purpose of radiotherapy is to destroy tumour cells. This means that at the tumour location radiation exposures are quite high, amounting to equivalent doses of 10 Sv or more. Inevitably, other tissues, including bone marrow, are also exposed, albeit to a much lesser extent. As has been mentioned above, studies on therapeutic exposure have provided data about the relationship between ionising radiation exposure and childhood leukaemia.[72,75]

The population exposure from diagnostic applications of imaging techniques has increased quite strongly.[79,95,96] An important driver for the recent increase is the use of computed tomography (CT) scans, which, by providing three-dimensional images, has considerable medical advantages, but which has also led to an increase of exposure, in terms of the number of examinations as well as an in the exposure per examination as compared to classical radiography.[97,98] With new digital imaging opportunities presenting themselves (such total body CT, cone beam CT, hybrid technology), and given market trends, expanding use of CT could further increase medical exposure substantially.

In 2009, the effective dose due to medical applications of ionising radiation (mainly diagnostics) was about 0.9 mSv per person per year, averaged over the whole population, in the Netherlands.[99] As compared with 2005, the exposure has nearly doubled, mainly due to CT scans. In Belgium, medical radiation exposure was considerably higher than in the Netherlands. The corresponding population average effective dose was 1.7 mSv in 2003 and 1.9 mSv in 2007.[100]

As radiographic exposures are not uniformly distributed over the body, the bone marrow equivalent dose will be different from the effective dose. However, the Committee considers that the numbers given above should be indicative of the bone marrow dose (per person per year, averaged over the whole population).

Because of the high radiosensitivity of red bone marrow in childhood, prenatal exposure and postnatal exposure in the first years of life are especially relevant. However, exposure data, specifically for prenatal exposure, are almost not available.

World-wide data collected by UNSCEAR for the period 1997-2007 resulted in an estimate of 3-10% of children in the age group of 0-15 years exposed to various radiographic examinations.[101] From an analysis of Dutch insurance data, it may be concluded that the frequency of these examinations strongly increases

with age.[102] This implies that average exposures later in life are higher than those at a younger age.

Epidemiological evidence

Epidemiological studies indicate that maternal exposure to X-rays during pregnancy is associated with childhood leukaemia.[75,76,103]

Recently, the authors of a retrospective cohort study concluded that the use of CT scans in children and young adults (<22 years of age) may almost triple the risk of leukaemia.[104] Data on the leukaemia risk related to frequent X-ray exposures during neonatal intensive care is lacking.

Evaluation

The Committee concludes that the epidemiological evidence on medical radiation exposures lends support to the general conclusion that ionising radiation may cause childhood leukaemia.

Public health relevance

Radiotherapeutic exposures of children may cause secondary cancers, including leukaemia. As childhood cancer is relatively rare, the absolute number of cases will be small as compared to the total number of childhood leukaemias in Belgium and the Netherlands. From the scarce data on prenatal and postnatal (mainly diagnostic) medical exposures, the Committee concludes that the contribution nonetheless is relevant. However, any quantification of the risk is at present not possible.

Recommendations

Exposure to radiation for medical purposes needs to be justified, both collectively (is the method as such justified?) and individually (is the patient's examination or treatment justified?). The individual justification is the primary responsibility of the referring medical practitioner. Although clinical benefits should outweigh the small absolute risks, radiation doses, specifically from CT scans, ought to be kept as low as reasonably achievable (ALARA*), and alternative procedures which do not involve ionising radiation should be considered.[104]

It is broadly accepted that medical diagnostic exposures can often be reduced by increasing risk awareness among medical practitioners, and by applying 'optimisation' and diagnostic reference levels, without losing diagnostic

* ALARA (As Low As Reasonably Achievable): a principle intended to guide action to reduce exposure to harmful agents, such as ionising radiation.[12]

advantages.[79,96,105-107] The Superior Health Council in Belgium suggested to improve risk awareness of medical staff in order to better manage the risk related to digital imaging.[96] The Committee strongly supports this view and is of the opinion that it also needs to be applied with respect to prenatal and postnatal exposure, in view of the increased leukaemia risk*.

First and foremost, the choice of an imaging technique is important, weighing the diagnostic benefits against potential harms. The use of techniques that do not involve ionising radiation (magnetic resonance imaging, ultrasound) should always be considered, especially where pregnant women, infants and young children are concerned. A susceptible subgroup that may require special attention are prematurely born children.[109,110] As neonatal chest images are frequently required to investigate life-threatening lung diseases, optimisation in terms of X-ray exposure is necessary. Health care professionals may contribute to this cause by developing better techniques for radiology in children**. Furthermore, practitioners need to discuss the risks of radiation exposure with patients.

To resolve gaps in knowledge, there is a need for more detailed and more precise data on the exposure of unborn children and infants, including subgroups such as prematurely born children, in order to apply dose reduction strategies for X-ray examinations in pregnant women and infants. In addition, research is needed on the biological effects of pre- and postnatal diagnostic X-ray exposure in general and exposures from CT scans in particular.

5.1.5 *Parental occupational radiation exposure*

In various occupations workers are exposed to ionising radiation. In terms of average radiation exposure, the most important occupations are the nuclear industry (from mining to waste treatment), health care and industrial radiography.[111] The average registered effective dose of monitored workers in the Netherlands in 2004 was 0.6 mSv per person.

Although the average registered individual occupational exposure is generally low (an effective dose of 1 mSv or less), there are groups with much higher individual exposures. Examples are interventional cardiology personnel and groups of workers in nuclear power plants.[111]

Aircraft crews have also been identified as being occupationally exposed.[60,112-114] Depending on the nature of the flights, geographical location and the number of hours in the air, the increased exposure (effective dose) to

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* The Committee draws attention to an initiative in a quality improvement program for CT scans in children, an on-line learning tool for radiologists: the 'Image Gently' Campaign of The Alliance for Radiation Safety in Pediatric Imaging.[108] The Federal Agency of Nuclear Control in Belgium is a member of The Alliance.

** In 2012, the Dutch Health Inspectorate started a project on radiology in children. The aim is to enhance safer methods for radiological examinations in children.

cosmic radiation may amount to several mSv per person per year*.[115] The average effective dose for aircraft crew members in the Netherlands in 2004 was 1.5 mSv. This is comparable to Belgium, where average values of 1.3-1.6 mSv were established in the period from 2008 to 2010.[116]

Given the established relation between exposures to ionising radiation and childhood leukaemia and the fact that leukaemia can arise prenatally, exposure of radiation workers was studied as a potential risk factor for the development of childhood leukaemia in the offspring.

Epidemiological evidence

An epidemiological study on childhood leukaemia in the vicinity of the Sellafield nuclear complex (UK) showed an association with preconceptional occupational exposure of the fathers of children with the disease.[117] The findings were not confirmed, however, in further studies. The present consensus is that this exposure pathway is unlikely to explain the original association between childhood leukaemia in Sellafield and paternal preconceptional irradiation.[90] In a national record linkage case control study in the UK, excluding the Sellafield cases, the significantly increased risk of leukaemia among children of male radiation workers appeared not to be related to their preconception radiation dose.[118] Indeed, the association was greatest for the group with zero dose or doses below the level of detection.

The same study did not indicate that children of female radiation workers have a significantly increased risk of developing leukaemia.[118,119] The Committee is not aware of other epidemiological data on childhood leukaemia in relation to pre- and postconceptional occupational radiation exposure of women, including aircraft crew.

Evaluation

The Committee concludes that the epidemiological evidence for an association between parental occupational radiation exposure and childhood leukaemia is *inadequate*.

Public health relevance

On a population level, the contribution of occupational exposure to the incidence of childhood leukaemia will be quite small, because of the number of parents involved in work where exposure occurs and due to the radiation protection measures and the relatively low exposures.

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* E.g. for a return flight from Europe to Japan the effective dose is circa 0.1 mSv.

Recommendations

Occupational radiation exposure of pregnant women needs to be restricted. According to European regulations, exposure of the foetus should be less than an equivalent dose of 1 mSv, and registered radiation workers are obliged to declare a pregnancy to their employer.[112] Many employers then shift pregnant radiation workers to an alternate job, in which no exposure occurs.

Because of the potential risks of radiation exposure during the first weeks of pregnancy, the Committee recommends radiation workers and aircraft personnel to also notify their employer of the *intention* to get pregnant. In any case, employers should adhere to the accepted approaches for reduction of radioactive exposures, such as ALARA, and employees should be aware of the relevance of preconceptional care.

5.1.6 Residential proximity to nuclear installations

The possibly increased incidence of childhood leukaemia near nuclear installations is a recurrent social issue*.[6,121] The most recent input were the findings in a French study that reported a possible excess risk of acute leukaemia in children in the close vicinity of French nuclear power plants.[122]

Epidemiological evidence

Many studies have been performed to gain clarity on the relationship between living near nuclear installations and childhood leukaemia. One of the reasons for such studies came from observing clusters of childhood leukaemia cases near these installations. The research hypothesis usually is concerned with radioactivity released into the local environment, exposure to which might lead to an increase in health risks in general, and to a higher cancer and leukaemia risk in particular.

A recent report of the British Committee on Medical Aspects of Radiation in the Environment (COMARE)[123] refers to two reviews[124,125] that performed a meta-analysis by combining data from different studies. From the analysis of release data from nuclear power plants in the UK, France, Germany and Switzerland, COMARE concluded that equivalent doses related to radioactive releases are too low to explain a possible increase in leukaemia risk, given the present understanding of the biological impact of ionising radiation. It also rejected suggestions that the risk from exposure of the foetus to released tritium

* The issue was preceded by a debate on a fall-out related increased mortality of babies and young children due to the atmospheric atomic bomb tests.[120] Such claims were refuted in the course of the years, but, with the expansion of nuclear electricity production, the discussion reignited and focused on childhood leukaemia.

and radioactive carbon (as suggested by Fairlie[126]) could be much higher than currently assumed.[123]

Using the terminology the Committee has chosen in this report, COMARE can be said to conclude that the evidence for an epidemiological association between an increased leukaemia risk and a release of radioactivity in the local environment is *inadequate*, and that the higher incidence cannot be explained by airborne radioactive exposure. Therefore no evidence is known for a causal relationship.

The German Commission on Radiological Protection (Strahlenschutzkommission) has drawn a similar conclusion, based on the German KiKK* study.[127,128] A systematic review of French researchers was also unable to draw a conclusion about a possible cause for the increased incidence of childhood leukaemia sometimes observed in the vicinity of nuclear power plants.[129]

Recently, the results of an investigation into the incidence of childhood leukaemia and thyroid cancer in Belgian communities near nuclear installations became available.[130] Results showed no increase in the incidence of acute childhood leukaemia within a circle of 20 kilometers around five nuclear installations, except for one. In the latter site the incidence was higher than the national average, however based on a relatively small number of observed cases (n=21). Dose-response analyses were hampered by the relatively large size of the smallest administrative level at which cancer data are available in Belgium. Therefore it was recommended to participate in international collaborative initiatives to pool data on childhood leukaemia.

A problem in all these investigations is that the exposure of members of the population under study was not measured. Therefore, many studies used the distance from a dwelling to the nuclear installation as an exposure proxy, carrying out model calculations based on data of estimated releases of radioactivity as declared by the operator of the installation. These usually resulted in very low exposures. On this point, the Committee wishes to remark that the releases of noble gases from nuclear installations may vary by more than a factor 100, and that more or less instantaneous accidental releases of noble gases, often not registered, may be of more importance than the average annual release reported by nuclear installation operators. In addition, exposure quantities other than the usual equivalent dose may be more relevant in studying an association between childhood leukaemia and nuclear installations.

Evaluation

The Committee concludes that at present, the increased risk of childhood leukaemia near some installations, observed in some studies, has not been

* KiKK: Kinderkrebs in der Umgebung von Kernkraftwerken.

explained satisfactorily. Exposure to radioactive emissions seems an unlikely explanation, but uncertainties remain, especially with respect to the relevant exposure quantity and pattern.

Public health relevance

If there would indeed be an increased risk of childhood leukaemia when parents and young children live near a nuclear installation, the total number of cases in Belgium and the Netherlands will most likely be very small as compared to the total number of cases of childhood leukaemia in each country.

Recommendations

It is questionable whether the issue of a relationship between childhood leukaemia and living in the vicinity of a nuclear installation can be resolved by further epidemiological research, as long as meaningful exposure quantities (for radiation or other factors) have not been identified. Still, the Committee proposes to monitor the emissions of radioactive noble gases from nuclear installations, and to study locations that differ in the way emissions of radioactive noble gases are handled and locations with accidental releases of radioactive noble gases.

It might also be helpful to pool epidemiological data on potential risk factors related to the vicinity of nuclear power plants at an international scale, as has recently been proposed on the basis of studies in France and Belgium.[122,130,131] In any case, operators should adhere to the accepted approaches for reduction of radioactive emission, such as ALARA, using the best available techniques.

5.1.7 Radiation accidents

A recent UNSCEAR report listed about 350 radiation accidents.[132] The accidents are not limited to one sector, but occur with all applications of ionising radiation. Some are rather localised and involve overexposure of a few people, others may have impact on a much more extended scale, such as in the case of the Chernobyl accident in 1986.[133] In addition, criminal use of radiation has been reported. According to UNSCEAR, medical radiation incidents and accidents might be underreported.

Localised accidents leading to high radiation exposures may locally cause severe radiation sickness and death. In the case of accidents with a more extended release of radioactive substances into the environment, the exposures are much less, in any case at larger distances from the release point. In those situations, the question about a possible contribution to the incidence of childhood leukaemia arises. In Belgium and the Netherlands this was the case with respect to the Chernobyl accident.

Epidemiological evidence

The consequences of the Chernobyl accident have been reviewed by UNSCEAR several times, most recently in 2008.[134] UNSCEAR concluded that epidemiological studies among the population in the most severely contaminated areas in the Ukraine, Belarus and Russia showed an increased incidence of thyroid cancer, but not of other types of cancer. However, a more recent report described an increase in childhood leukaemia cases (ALL and particularly AML) in the most severely contaminated areas of the Ukraine.[135,136] However, there is uncertainty about the quality of the data and therefore about the magnitude of the radiation risk.[137]

Evaluation

Based on an increase in childhood leukaemia cases in the most severely contaminated areas of the Ukraine, the Committee concludes that the evidence for an association between exposure from radiation accidents and childhood leukaemia in general is *limited*.

Public health relevance

In Belgium and the Netherlands, the exposure to radioactive substances released in the Chernobyl accident is not reflected in increased cancer risks observable from cancer registers or dedicated epidemiological research. In low exposed European countries such as Belgium and the Netherlands (average whole-body dose <0.2 mSv) the attributable fraction of all leukaemia cases, including childhood leukaemia cases, due to radiation exposure from the Chernobyl accident has been estimated at about 0.01%.[138] This is too low to be detected epidemiologically. This study contradicts the conclusions of an earlier report that Chernobyl fallout could well have caused a small, but significant excess of childhood leukaemia cases in Europe, in view of the excess cases in the birth cohort exposed in utero.[139]

Looking at a population level, the Committee adheres to the view that the impact of remote accidents where ionising radiation was released on an extended scale, as was the case in Chernobyl, has been undetectable in Belgium and the Netherlands. Local accidents, however, will always incur some risk, dependent on the exposure situation.

5.1.8 *Overall conclusions and recommendations*

Conclusion

On the basis of epidemiological and laboratory research as reviewed by international and national expert committees, the Committee concludes that prenatal and postnatal exposure to ionising radiation contribute to the incidence of childhood leukaemia. Because of this, the Committee considers a causal relation between exposures to ionising radiation and childhood leukaemia as **established**.

In addition, the Committee supports the view expressed by several multidisciplinary Committees of scientists that this holds for all types of ionising radiation, and that there is no exposure threshold below which an increase in leukaemia risk is absent.[59,60,73,78,79]

Of the specific exposure situations considered, the Committee believes that exposure to natural radiation may provide a non-negligible contribution to the incidence of childhood leukaemia. Exposure for medical reasons and the projected increase in this area, especially from CT scans for diagnostic purposes, is a specific matter of concern. Other widespread types of exposures, e.g. those of pregnant passengers and young children during flights, are thought to contribute only marginally to the risk of childhood leukaemia, both individually and on a population level.

Recommendations

Despite the overall risks being small, exposure reduction is warranted in the medical as well as in the environmental and occupational fields, not only to reduce childhood leukaemia, but also to reduce the occurrence of other adverse health effects.

The possibilities for the reduction of exposure to ionising radiation will vary in different situations, and will also vary in Belgium and the Netherlands. Notwithstanding the large uncertainties, the contributions of natural and medical sources of ionising radiation exposure are the most relevant, and a reduction in the exposure to these sources may be expected to decrease the risks. Effective ways to achieve this may be: stricter justification standards and optimisation procedures for medical exposures, further reduction of emissions from nuclear installations and continuing or intensifying radon reduction programmes. The Committee emphasises that exposure reduction is not only important for leukaemia, but also for other forms of cancer and other diseases associated with exposure to ionising radiation.

5.2 Extremely low-frequency (ELF) magnetic fields

Exposure to ELF magnetic fields is highly dependent on location and time. Major indoor sources are the indoor electricity system and electrical appliances. Magnetic fields are only generated when current flows, and their strengths are therefore directly dependent on appliance use. The fields decrease in general with the square or the 3rd power of distance, so the magnetic field strength may vary considerably over short distances.

The primary external source in Belgium and the Netherlands are overhead high voltage power lines. Their contribution to total exposure is relevant within a distance of up to approximately 150 m from the line, and also depends on the amount of current transported and the voltage on the line. Since the first report suggesting an association between living in the vicinity of power lines and childhood leukaemia was published in 1979, dozens of increasingly sophisticated studies have examined the possible association with exposure to ELF magnetic fields.[140]

Evidence

Based on consistent associations found in individual epidemiological studies and the results from two pooled analyses, in 2002 IARC classified ELF magnetic fields as 'possibly carcinogenic to humans' (group 2B: see Annex F).[140] In 2007, a WHO expert task group concluded that consistent epidemiological evidence suggests that chronic exposure to low-intensity ELF magnetic fields ($\geq$0.4 μT* as compared to <0.1 μT) is associated with an increased risk of childhood leukaemia.[18] Both major reviews were taken into account in both Evidence Summaries of systematic reviews.[213,225] A drawback of both reviews, however, is that the residential exposure to ELF magnetic fields was not defined uniformly. It varied from 24-hour or instantaneous measurements in one or more rooms, distance and relative load for power lines to exposure from different electrical appliances.[18,140]

The results of a more recent pooled analysis by Kheifets et al. of seven studies published since 2000 are in line with the outcomes of previous pooled analyses, which showed an association between measured or calculated magnetic fields and childhood leukaemia in general.[141] The association seems weaker in the most recently conducted studies, but these are small and lack the methodological improvements needed to clarify the apparent association.

Although some experimental studies report effects of ELF on mutation frequency and gene expression, the WHO task group concluded that there is limited evidence for a causal relation.[18]

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* The strength of magnetic fields is expressed in the magnetic flux density in microtesla (μT).

Evaluation

Many epidemiological studies have focussed on the association between residential exposure to ELF magnetic fields from power lines or electric appliances and childhood leukaemia. Most of these have considered childhood leukaemia in general; consequently separate information on ALL and AML is very limited. Since more than 80% of childhood leukaemia is ALL, the Committee considers the association to be applicable to this most common form, although it cannot be ruled out that the association could be due to a combination of selection bias and confounding.[14,142] Therefore, the Committee considers the epidemiological evidence for an association between exposure to ELF magnetic fields and ALL (and childhood leukaemia in general) *sufficient*, whereas for AML it is characterised as *inadequate*.

The epidemiological findings are insufficiently supported by results from experimental studies and by mechanistic insights into causality, which means that the plausibility of there being a biological mechanism should be considered *low*.

Based on the available evidence from these two types of research, the Committee considers a causal relation between exposure to ELF magnetic fields and ALL or childhood leukaemia in general as **possible,** whereas the existence of a causal relation between ELF magnetic fields and AML is **unknown**.

Public health relevance

The number of children exposed to ELF magnetic field levels above which an increased risk of childhood leukaemia is observed in epidemiological studies (exceeding 0.4 μT) is small. A survey in Belgium indicated that the prevalence of children exposed to at least 0.4 μT is approximately 1.4% for modelled exposure from overhead power lines and 4% for measured exposures from power lines and other sources.[143]

No such data are available for the Netherlands. For the Netherlands it was calculated in 2003 that approximately 11,100 children live in areas near overhead high power lines where the magnetic field strengths exceed 0.4 μT.[144] Assuming a total number of children up to age 15 of approximately 3 million, the exposure prevalence in the Netherlands is approximately 0.4%.[144,145] Ahlbom et al. calculated a relative risk for exposure levels of at least 0.4 μT, compared to levels of less than 0.4 μT, of 2.00 (95% confidence limits 1.27-3.13).[146]

Combining these data into the formula given in section 2.3 of this report results in a population attributable fraction (PAF, expressed as a percentage) for Belgium of 1.38 (0.38-2.90)% for modelled and 3.85 (1.10-7.85)% for measured exposures and for the Netherlands a PAF of 0.40 (0.11-0.84)% for modelled exposures (measured exposures not available). The maximum additional

individual risk to develop leukaemia for children in the Netherlands was found to be $3x10^{-5}$ per year.[144,145]

Considering that an incidence of 3.8 per 100,000 was used, these data pertain to ALL only. This means that, if a causal relation exists, and given a total of approximately 110 new ALL cases each year, the number of extra cases of ALL attributed to magnetic exposures from high voltage power lines in the Netherlands is estimated at 0.4-0.5 per year.[144]

Recommendations

If the relation between exposure to ELF magnetic fields and childhood leukaemia would be causal, its impact is likely to be small at the level of the general population. However, in situations where children are long-term exposed to magnetic fields exceeding approximately 0.4 μT it might be relevant. This warrants taking precautionary measures for these high-risk groups to reduce exposures.[8]

5.3 Radiofrequency radiation

In the past decades, exposure of the population to radiofrequency electromagnetic fields (RF EMF) has been ubiquitous. Radio- and television transmitters have increased in number and become more powerful. The rise of mobile telephony has added another layer of RF EMF to society. Several studies have investigated a possibly increased incidence of childhood leukaemia near sources of RF EMF.

Evidence

No systematic reviews on the association between radiofrequency radiation and childhood leukaemia have been identified. Individual studies are all hampered by difficulties in assessing the exposure. This is especially problematic since exposure is highly variable, depending on frequencies and types of signals.[147]

In its 2005 Electromagnetic Fields Annual Update, the HCN discussed the available epidemiological studies on cancer incidence near radio and television transmitters.[148] Several included childhood leukaemia. The HCN concluded that the overall picture emerging from these studies shows that there is insufficient evidence to establish an association between living in the immediate vicinity of a radio or television transmitter and increased risk of leukaemia or any other form of cancer.[148]

A more recent case-control study found no association between childhood leukaemias (and other early childhood cancers) and the estimated RF exposure from mobile telephone base stations of the mothers during pregnancy.[149]

Recent reviews of experimental studies indicate a *low* plausibility for a causal relation.[150,151]

Based on indications for an increased risk for glioma, a malignant type of brain cancer, associated with mobile phone use, in 2011 IARC has classified RF EMF as 'possibly carcinogenic to humans' (group 2B).[152] Data on childhood leukaemia were not provided.

Evaluation

There is *inadequate* epidemiological evidence that pre- or postnatal exposure to RF EMF does increase the risk of childhood leukaemia, and the plausibility of a causal biological mechanism is *low*. The Committee therefore considers the existence of a causal relation between exposure to RF EMF and childhood leukaemia to be **unknown**.

Recommendations

Since the general trend is likely one of increasing exposures, more insight in actual exposures is recommended. Further research on the potential association between RF EMF and childhood leukaemia is not considered to be a high priority.

5.4 Diagnostic ultrasound scans during pregnancy

Ultrasound is a commonly used imaging modality during pregnancy, and is generally regarded as safe to the foetus.[153] Current ultrasound technology, however, has a significantly higher output potential than the older machines used in most clinical studies, and the safety profile of the increasingly frequent use of Doppler, 3-dimensional (D) and 4-D ultrasound with modern machines is unknown. Since ultrasound is a form of energy, it has the potential to produce biological effects that may constitute a risk for health.[154] Prenatal diagnostic ultrasound scans are increasingly used during pregnancy.[153] In the Netherlands, a routine ultrasound scan is offered to all pregnant women in the first and the second trimester of the pregnancy, the latter having been added in 2006.[155] In Belgium, three standard ultrasound scans are offered per pregnancy. Ultrasound exposure of the mother has also been investigated as a possible causal factor for childhood leukaemia.

Evidence

Information on the possible effects of ultrasound exposure in utero on the incidence of ALL or AML is not available, and the systematic analysis identified only three studies on childhood leukaemia in general.[156] Neither higher or lower

risks were observed. A more recent systematic review carried out by the WHO concluded that ultrasound in pregnancy was not associated with childhood leukaemia nor with other adverse health effects.[154] In a recent case-control study, logistic regression models which adjusted for maternal age and child's birth weight also showed no evidence of increased risk of childhood cancer due to in utero exposure to ultrasound scans.[157]

Experimental evidence has shown that ultrasound is capable of inducing double strand breaks in DNA, but this only occurs only at higher energy levels than the ones used in diagnostics.[158]

Evaluation

Considering the available diagnostic imaging techniques, ultrasound offers the best possibilities to reduce exposure to medical ionising radiation. According to the epidemiological evidence, exposure to diagnostic ultrasound during pregnancy appears to be safe. However, new experimental data indicates that DNA can be mechanically damaged, albeit at higher levels than used in diagnostic ultrasounds.

The available epidemiological data does not support a potential causal relation between the current diagnostic ultrasound exposure and the risk of childhood leukaemia, neither does the scarce experimental data (only available at higher energy levels than used in diagnostics). Therefore, the Committee considers a causal relation between the limited exposures to routine diagnostic ultrasounds and childhood leukaemia **unlikely**. Ultrasound exposure can be assumed to rise, both in frequency and in level. Whether a causal relation may exist between more frequent and higher level exposures and childhood leukaemia is **unknown**.

Recommendations

Since ultrasound scans are offered to all pregnant women in the first and second trimester of pregnancy, exposure is very common. Since technical developments may be expected to result in higher exposure levels, possible adverse effects of more intensive or frequent ultrasound scans, e.g. following in vitro fertilisation (IVF), warrant further research, and the recommendation that ultrasound scans should not be offered without medical indication.

6 Chemical environmental factors

In this chapter the role of chemical risk factors on the induction and development of childhood leukaemia is evaluated. These include pesticides, benzene, organic solvents other than benzene, arsenic in drinking water, parental tobacco smoking, parental marijuana smoking, parental alcohol consumption, maternal intake of cured meat, and other chemicals.

6.1 Pesticides

'Pesticides' is a generic term used for a great number of chemical preparations. Over the last decades, several hundreds of pesticides have been marketed for agricultural or domestic use. They consist of biologically active ingredients commonly used to control unwanted organisms in agricultural and residential (indoor or outdoor) environments, and are grouped or classified according to the pests they control (i.e. insecticides, herbicides, fungicides, rodenticides), their application (plant protection products or biocides), their chemical structure (organic or inorganic), how/when they work (i.e. contact, systemic, residual, etc.) or their mode/site of action (i.e. inhibitors of acetyl CoA carboxylase, inhibitors of acetyl cholinesterase, etc.).

Pesticides are widely used: they protect agricultural crops against disease and infestation, they remove weeds from pavements, and they combat vermin in and around homes. They may, however, also be harmful to other than the target organisms. And they may have unwanted effects on human health. Some pesticides can cause short-term (acute) as well as long-term (chronic) adverse effects, including cancer. There are three main routes of exposure to pesticides: oral, dermal, and inhalation.

Pesticide exposure

Given their widespread use, pesticides are ubiquitously present in our environment and humans are inevitably exposed: the general population (adults and children) come into contact with the residues of pesticides in air, water and food, and occupational groups may be exposed at all stages of pesticide formulation, manufacturing, application or re-entry. The level, however, varies according to the patterns of exposure. Individuals who personally apply pesticides in agricultural, occupational or residential settings are likely to experience the highest levels, whereas indirect exposure to residues of pesticides

through drinking water, air, dust and food is likely to result in low-level exposures.[159]

Exposure scenarios vary greatly among groups and across the world. Low amounts of pesticides (residues) can remain in or on a crop after harvesting or storage and make their ways into the food chain. That is why they are only allowed onto the market after an extensive safety assessment.[160] In many countries, Belgium and the Netherlands included, accepted levels of residues in food are controlled by regulatory bodies.

A recent study, based on the 2008 surveillance data of the Belgian Federal Agency for the Safety of the Food Chain, has demonstrated that for most of the pesticide residues in fruits and vegetables, the chronic exposure of the adult population is 100 times lower than the 'acceptable daily intake' (ADI)*. With regard to children, however, there are indications that for some pesticides** the ADI can be exceeded.[161]

Children can be exposed to pesticides from various sources: indirectly via parental (occupational) exposure, but also directly via residential exposure, e.g. from indoor use (biocides in homes, schools or other buildings), from outdoor use (garden, playing areas/public lands, agricultural application drift, overspray or off-gassing), through residues in food and drinking water, by handling pets treated or contaminated with biocides or other pesticides, or by other routes (e.g. through the use of insecticidal shampoos for lice infestation).[162] Three critical time windows of exposure are relevant to the effects of pesticides in children: exposure of the parents prior to conception, exposure of the mother during pregnancy, and exposure of the child after birth.

Pesticides have been particularly scrutinised as potential aetiological factors in childhood leukaemia.[9,163-165] Discrepancies among epidemiological studies have made it especially important to conduct systematic reviews and meta-analyses.[166-170] In the following sections the Committee provides a brief overview of these reviews.

Epidemiological evidence on parental occupational exposure

Indirect exposure of children through occupational exposure to pesticides by adults in the reproductive age may substantially exceed the exposures from other sources.[166]

Systematic reviews, one included in the CCG Evidence Summary[166] and one published later[168], indicate increased risks for ALL, AML and childhood leukaemia in general following prenatal maternal occupational exposure to pesticides, although not reaching statistical significance for ALL in one review.[168] The associations with paternal occupational exposure to pesticides

* ADI: measure of the amount of a specific substance in food or drinking water that can be ingested on a daily basis over a lifetime without an appreciable health risk.

** For genotoxic carcinogens no ADI can be derived.

before conception were weaker, and no significantly increased risks were observed for ALL, AML or childhood leukaemia in general.

A third more recent meta-analysis observed different results, as paternal exposure was associated with a significantly increased risk of childhood leukaemia.[170] However, these results have to be viewed with caution, since several overlapping datasets were included. Therefore, the results cannot be reasonably compared with those of the other meta-analyses*.

Epidemiological evidence on residential exposure

Residential pesticide use, defined as indoor or outdoor domestic use of pesticides, is associated with elevated exposure of children.[167] Systematic reviews, one included in the CCG Evidence Summary and one published later, investigated residential pesticide exposure during the three critical time windows: preconception, pregnancy and childhood.[167,169] Studies on the proximity to agricultural activities were not included in these meta-analyses.

Significantly increased risks associated with exposure during pregnancy were observed for ALL in both reviews, and for AML in one review.[169] During childhood no significantly increased risks for ALL and AML were found. However, both reviews did report statistically significant associations between childhood leukaemia in general and exposure during pregnancy, as well as during childhood.[167,169]

A third more recent meta-analysis reported significantly increased risks for childhood leukaemia in general connected with parents' use of pesticides in the home or garden.[170] This is in agreement with the results of the two earlier systematic reviews.

As in the previous section, however, the Committee considers that these results need to be viewed with caution, since several overlapping datasets were included and the results therefore cannot be reasonably compared with those of the other meta-analyses.

One more systematic review investigated whether professional pesticide treatments (i.e. pest control) in or around the home before birth or during childhood increased the risk of childhood ALL.[171] An increased risk of borderline statistical significance was observed when pesticide treatment was applied during pregnancy. The results for treatments carried out between birth and diagnosis were similar, and slightly lower.

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* Some methodological aspects of this meta-analysis are of questionable value: the authors have extracted several risk estimators (and variances) from each individual study, rather than one estimator per study, to compute the summary effects in the meta-analyses.[163] This renders it impossible to rigorously compare the results with those of the other meta-analyses.

Other evidence

In 1991, IARC evaluated the carcinogenic risk to humans posed by occupational exposure during the spraying and application of insecticides, on the basis of the epidemiological and experimental studies.[172] The volume also features separate monographs evaluating the carcinogenicity of 17 individual pesticides, including several that have been banned by industrialised countries, but that are still in use in the developing world. Although some of these pesticides have been applied for more than four decades, evaluations of carcinogenicity were hindered by the scarcity of well-designed epidemiological studies.

The first and most extensive monograph was dedicated to an evaluation of data from various epidemiological studies suggesting an increased risk of cancer, most notably lung cancer, multiple myeloma and other tumours of B-cell origin in workers exposed to insecticides during their application. On the basis of this, IARC concluded that the spraying and application of non-arsenical insecticides entail exposures that are 'probably carcinogenic to humans'.

In the remaining monographs an evaluation was carried out of the carcinogenicity of aldicarb, atrazine, captafol, chlordane, DDT, deltamethrin, dichlorvos, fenvalerate, heptachlor, monuron, pentachlorophenol, permethrin, picloram, simazine, thiram, trifluralin, and ziram*. Of these, captafol, a fungicide used on plants for seed treatment and as a wood preservative, was classified as 'probably carcinogenic to humans'. Atrazine, chlordane, DDT, dichlorvos, heptachlor and pentachlorophenol were classified as 'possibly carcinogenic to humans' (see Annex F). The remaining pesticides could not be classified on the basis of available data. Among these are deltamethrin, picloram, thiram and ziram, which are still approved in EU countries.

More recently, several pesticides appeared to be able to change gene expression through a broad array of gene regulatory mechanisms, including regulation of gene translocation, DNA methylation or DNA repair.[173]

Causality considerations

As there is a lot of controversy and debate with regard to the role of pesticide exposure in childhood leukaemia, and the available information appeared to be not unequivocal, the Committee followed explicitly the well-established Bradford Hill considerations to evaluate, as objectively as possible, the available scientific evidence that pesticide exposure may cause childhood leukaemia (see also Annex E).[14,15]

Strength. Inherent to most environmental factors, the observed associations between pesticide exposure through parental occupational exposure or

* Of these, aldicarb, atrazine, captafol, chlordane, DDT, dichlorvos, fenvalerate, heptachlor, monuron, pentachlorofenol, permethrin, simazine and trifluralin are no longer approved in EU countries.

residential exposure and childhood leukaemia were mostly weak and only barely significant.

Consistency. Although all meta-analyses showed a tendency toward increased risk (except in the case of paternal occupational exposure and AML), discrepancies were observed in statistical significance. This might argue against a causal relationship. For childhood leukaemia in general, the statistically significant associations with pesticide exposure during pregnancy (via maternal occupational or residential exposure) observed in the different meta-analyses tends to support a causal relationship. It has to be stressed, however, that the individual studies included in the different meta-analyses are largely the same ones, and the consistency in the results is therefore not surprising.

Specificity. The ability to associate specific pesticide exposures with specific childhood cancers is limited by both the low prevalence of childhood cancer and the imprecise exposure assessment. The aetiology of childhood leukaemia is likely multifactorial, resulting from the effect of either genetic or environmental factors, and, probably, from their interaction. Conversely, pesticide exposure is not uniquely associated with childhood leukaemia.

Temporality. While it is obvious that, given a causal relationship, an exposure to a risk factor should occur before childhood leukaemia develops, it is not clear in which time window it would exert its causative action: prior to conception, during early, mid or late pregnancy or during childhood. However, maternal exposure to pesticides during pregnancy appears to be more consistently associated with childhood leukaemia than exposures during childhood.

Biological gradients. Many of the epidemiological studies did not attempt to assess cancer risks in response to increasing frequency or intensity of pesticide exposures. However, some authors tried to establish an exposure-response-like relationship between residential exposure to pesticides and childhood leukaemia in general.[169] Although they showed that, in most cases, the risk of leukaemia is increased with frequency of use, these observations provide only weak additional support to the suspicion of a positive exposure-response relationship between pesticide exposure and childhood leukaemia.

Plausibility. Pesticides are biologically active molecules that may play some role in cancer aetiology. The US Environmental Protection Agency (EPA) and other national and international bodies have identified about 165 active ingredients of pesticides as known, probable or possible human carcinogens, many of which have been banned or restricted.[174]

Evaluation

Due to limitations in the available research, including questions regarding exposure assessment and exposure-response, the epidemiological evidence that parental occupational and residential exposure to pesticides is associated with an

increased risk of childhood leukaemia in general is classified as *limited.* The most consistent evidence is for maternal exposures during pregnancy.

In spite of the scarcity of specific data on ALL, the Committee still considers the evidence for this type of leukaemia to be *limited*, as it is by far the most common type of leukaemia in children and data for leukaemia in general are heavily weighted towards ALL. It would therefore be unrealistic to conclude differently for leukaemia in general and for ALL.

The evidence regarding AML, on the other hand, is *inadequate*. The available studies are scarce, and some are of insufficient quality to allow for a robust conclusion on causality. In addition, the epidemiological evidence is based on data from case-control studies with, in most cases, poor characterisation of exposure. Chance, bias or confounding cannot be ruled out with reasonable confidence. Since several pesticides have been classified as known, possible or probable* human carcinogens**, causal relations with (past) exposures to (mixtures of) pesticides are *moderately to highly* plausible.

Based on the available evidence, which is scarcer for ALL and AML than for childhood leukaemia in general, the Committee considers a causal relation between exposure to pesticides and childhood leukaemia in general and ALL **possible to likely,** and a causal relation between exposure to pesticides and AML **uncertain to possible**. The Committee does not rule out that past exposure to specific (classes of) pesticides might play a greater role in the development of childhood leukaemia than others.

Public health relevance

Population attributable fractions (PAF) have been calculated for maternal occupational exposures during pregnancy***, ranging from 1% (for all types) to 4% (for ALL) and 5% (for AML). Residential exposures have been calculated to account for 17% (in the case of ALL), 25% (for all types), and 26% (for AML). This indicates that especially residential exposures are relevant, provided the relation with childhood leukaemia can be considered causal.

Recommendations

The Committee recommends reducing parental, and particularly maternal, occupational exposure to pesticides. Also, it recommends the monitoring of pesticide exposures among occupationally exposed women, at least of

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* Probable carcinogen (US EPA classification) or 'presumed' carcinogen (EU classification).

** 'Known' and 'presumed' carcinogenic pesticides will no longer be approved in EU countries.

*** Personal communication Van Maele-Fabry 2011: For occupational exposure, the data from the systematic review of Wigle et al. were used for ALL and AML (based on 1213 cases and 674 controls); for all types of leukaemia and for residential exposure, the data from the systematic review of Van Maele-Fabry et al. were used (based on 3386 controls).[166,168,169]

reproductive age, incorporating biomarkers of exposure whenever feasible. In general the Committee advocates preventive actions, including education and counselling, focused specifically on women of childbearing age, resulting in more risk awareness previous to intended conception. Furthermore, limiting the use of pesticides or biocides for residential purposes is recommended, in order to keep the exposure of pregnant women and young children as low as possible.

The possibility of simultaneous exposure to several pesticides with a common mechanism of toxicity and of simultaneous exposure to the same compounds from various sources, including food, merits systematic attention in the risk assessment of individual pesticides.[160] Finally, the Committee recommends to include young children in risk assessments.

6.2 Benzene

Benzene is a frequently used organic solvent and a component of gasoline, ubiquitously present in the environment, although in general in relatively low concentrations. In epidemiological studies occupational exposure to benzene has been associated with adult AML.[175] To a lesser extent associations have been found between environmental exposure situations and childhood leukaemia.

Evidence

Evidence for an association between benzene exposure and childhood leukaemia is accumulating. Multiple epidemiological studies have shown an increase in childhood ALL, and particularly in AML, nearby air pollution sources emitting benzene, such as gas stations and traffic.[176,177] However, the available reviews present different conclusions regarding environmental exposures.

IARC classifies benzene as 'carcinogenic to humans'.[178] This classification has been primarily based on the relation with adult AML found in occupational epidemiological studies. Although leukaemia in children (predominantly ALL) undoubtedly has some biological characteristics that differ from leukaemia occurring at a later age (predominantly AML), the pattern of 'microdeletions' of relevant genes in adult and adolescent leukaemia sufficiently resembles that in childhood leukaemia to suggest that, genetically speaking, adult, adolescent and childhood cases may be more similar than previously thought.[179]

Benzene may be leukaemogenic through genotoxic, epigenetic and other gene-regulatory mechanisms. It induces chromosomal abnormalities, epigenetic modifications, including changes in DNA methylation of genes related to carcinogenesis, which lead to changes in gene expression. Moreover, benzene has been observed to cause haematotoxic effects and to activate cell-cycle-regulating genes, resulting in compensatory formation of white blood cells.[180] These haematotoxic properties of benzene are also suggestive of leukaemogenic effects.[175,180]

More recently gained mechanistic insights lend support to the potential associations between benzene exposure and childhood leukaemia.[176]

Evaluation

The few available data from epidemiological studies on the relation between exposure to benzene and childhood leukaemia are not consistent, in part due to insufficient exposure data. However, the data on adult leukaemia do show consistent associations between occupational exposure to benzene and leukaemia, especially AML. Recently supporting mechanistic evidence has also become available.

Overall, the Committee considers the epidemiological evidence for an association of exposure to benzene and childhood leukaemia to be *limited*, and the biological plausibility of causality to be *high*. The Committee therefore considers a causal relation between exposure to benzene and childhood leukaemia to be **likely.**

Recommendations

In order to obtain more solid evidence on the possible causal relation between exposure to benzene and childhood leukaemia, targeted monitoring studies should be performed in situations where exposure may occur. In the meantime, the available evidence warrants taking measures to limit or prevent exposure of children and pregnant women to benzene. In particular counseling previous to intended conception may improve risk awareness of traffic exposures and other sources of benzene exposure of pregnant women and children.

6.3 Organic solvents other than benzene

Organic solvents are commonly used, for instance in gasoline or indoors as a paint thinner or in chipped wood (i.c. formaldehyde). This is a very broad category. For most solvents no information on possible effects on childhood leukaemia is available, therefore only some examples can be discussed.

Evidence

For a number of specific solvents epidemiological evidence is available that they might contribute to the risk of childhood leukaemia.[181-183] In a study among children with ALL, 15.2% showed specific genetic mutations that were related to maternal exposure to solvents.[184] However, a more recent review concluded that there is no consistent support for the claim that parental exposure to solvents and petroleum-based hydrocarbons is a causative factor in the development of childhood ALL or AML.[177]

For several other substances (including styrene and formaldehyde), only associations have been reported between adult exposures and adult leukaemia.[185-188]

In 1989, IARC classified diesel engine exhaust as 'probably carcinogenic to humans' and gasoline engine exhaust as 'possibly carcinogenic to humans'.[178] Petroleum solvents were considered as 'not classifiable as to their carcinogenicity to humans'. Occupational exposure as a painter was classified as 'carcinogenic to humans'. However, occupational exposure in paint manufacture was considered as 'not classifiable as to its carcinogenicity to humans'.

Formaldehyde is an established human carcinogen[178], known to induce chromosomal abnormalities in blood cells.[189] Styrene is classified by IARC as a 'possibly carcinogenic to humans'[178] and is associated in many epidemiological studies with cancers of the blood-forming organs and the lymphoid system in adults.[190] These substances might therefore potentially contribute to an increased risk of childhood leukaemia.

Evaluation

The Committee considers the available evidence from epidemiological studies *inadequate* as a basis for any conclusion on a relation between exposure to organic solvents other than benzene and childhood leukaemia. Without experimental data, it therefore considers a causal relation between most organic solvents and childhood leukaemia as **unknown**.

Since specific organic solvents such as styrene and formaldehyde have been classified respectively as 'possibly and established carcinogenic', the Committee considers the plausibility of a causal relation with childhood leukaemia for these solvents respectively as *moderate* and *high*. Therefore, the Committee considers a causal relation with exposure to specific organic solvents such as styrene and formaldehyde respectively as **uncertain** and **possible**.

Based on IARC evaluations, the Committee considers a relation with exposure to engine exhausts as *moderately to highly* plausible and occupational exposure to paints as *highly* plausible. Therefore she considers a causal relation with childhood leukaemia for engine exhausts **uncertain to possible** and for occupational exposure to paints as **possible**.

Recommendations

The application of volatile organic compounds with carcinogenic properties, such as styrene and formaldehyde, in materials commonly encountered in the living environment should be avoided. Reducing exposures to solvents, for instance during painting indoors, might also be beneficial for the prevention of other adverse health effects. In view of the scarcity of adequate information, there is a need for both epidemiological and experimental studies into the

relation between commonly encountered organic solvents and childhood leukaemia.

6.4 Arsenic in drinking water

Arsenic is widely occurring both naturally and as a result of human activity. Food is the main source of exposure for the general population in Europe.[191] Inorganic arsenic is produced primarily as a by-product from metal smelting processes.[192] Up to 70% of global arsenic production is used in the industrial preservation of wood, as chromated copper arsenate (CCA).

Arsenic combines with oxygen, chlorine, and sulphur to form inorganic arsenic compounds, which are more toxic. Inorganic arsenic compounds have been found as contaminants of drinking water worldwide. They enter drinking water supplies from natural deposits in the earth or from agricultural and industrial practices. Arsenic has been found to cross the placenta, and can cause foetal toxicity.[193]

The Joint FAO/WHO Food Standards Programme Codex Committee on contaminants in food has noted that drinking water is a major contributor to total inorganic arsenic dietary exposures and, depending on the concentration, can also be an important source of arsenic in food, through food preparation and possibly irrigation of crops.[194] For certain regions in the world, where concentrations of inorganic arsenic in drinking water are above the WHO guideline value of 10 µg/l, the FAO/WHO Committee has remarked that there is a possibility that adverse effects could occur. The provisional guideline value for a 'safe limit' for arsenic in drinking water has been adopted as a national standard worldwide, including the European Union.

Arsenic has been shown to cause cancer in human beings (e.g. lung, skin, bladder), but few studies have been conducted to assess whether arsenic exposure is also a risk factor for childhood cancers.[195]

Evidence

In two reviews, including one identified in the CCG Evidence Summary, no statistically significant increased risks for childhood ALL were observed in relation to high levels of arsenic in drinking water.[195,196]

IARC classifies arsenic and inorganic arsenic compounds as 'carcinogenic to humans'.[178]

Evaluation

The Committee concludes that there is *inadequate* epidemiological evidence that exposure to inorganic arsenic compounds in drinking water is associated with an increased risk of childhood leukaemia. Since arsenic and inorganic arsenic

compounds have been classified as carcinogenic, the biological plausibility for causality is considered *high*, however. As a consequence, the Committee considers a causal relation between exposure to inorganic arsenic compounds in drinking water and childhood leukaemia **possible**.

Public health relevance

In view of the ubiquitous potential of exposure to inorganic arsenic compounds by ingestion of drinking water, the relevance to public health is obvious. Even when the concentrations remain below the levels recommended by WHO, the resulting health problems are not negligible.[197] However, due to a lack of data the effect on childhood leukaemia cannot be estimated.

Recommendations

The Panel on Contaminants in the Food Chain (CONTAM Panel) has recommended that exposure to inorganic arsenic should be reduced.[191] The Committee endorses this recommendation. If this general recommendation is followed, there is no need for further studies on a possible relation between exposure to arsenic and childhood leukaemia.

6.5 Parental tobacco smoking

Another chemical factor that may enhance the risk of childhood leukaemia is parental tobacco smoking. The effects of passive smoke on cancers other than lung cancer are, however, still a matter of discussion.[198]

Evidence

A meta-analysis identified in the CCG Evidence Summary studying the association between the amount of parental tobacco smoking and childhood cancers showed inconsistent results with respect to risks for ALL and AML.[198] A more recent meta-analysis observed an increased cancer risk for any paternal smoking around the time of the child's conception and for smoking more than 20 cigarettes per day around that time.[199] As most studies of maternal smoking during pregnancy have reported no increased risks for the occurrence of childhood cancers, a meta-analysis for maternal smoking was not conducted.

IARC has classified (second-hand) tobacco smoke as 'carcinogenic to humans'.[178]

Evaluation

The Committee concludes that there is *limited* evidence that paternal smoking increases the risk of childhood leukaemia. Since there is ample evidence that tobacco smoke is carcinogenic, the Committee considers the biological plausibility *high* and a causal relation between paternal tobacco smoking and childhood leukaemia **likely**. For maternal smoking the epidemiological evidence is *inadequate*, so a causal relation in that case is **possible**. Causal relations with ALL and AML separately are **uncertain**.

Recommendations

Since parental smoking increases the risk of many disorders in embryos, foetuses and children (abortion, preterm birth, intra uterine growth retardation, congenital malformations, sudden infant death, asthma, allergy)[200], parents should be urgently advised to stop or avoid smoking before conceiving a child. It is advisable to do so at least three months before intended conception, and maintain this during and after pregnancy.

6.6 Parental marijuana smoking

Marijuana smoke contains several of the same carcinogens and co-carcinogens as the tar from tobacco, raising concerns that smoking marijuana may be a risk factor for tobacco-related cancers and, possibly, for childhood leukaemia.[201]

Evidence

In a review included in the CCG Evidence Summary, the association between the frequency, duration, amount, mode and period of marijuana use (ever, preconceptionally, during pregnancy or current) and cancer risk was looked into. In one study maternal use of marijuana during pregnancy or in the year before pregnancy was found to be associated with an increased risk for AML.[201] However, no other studies corroborated this finding.

Evaluation

The available epidemiological data provide *inadequate* evidence that parental use of marijuana during or in the year preceding pregnancy increases the risk of childhood AML. In view of the known toxic properties of cannabinol derivatives, however, the Committee considers a causal mechanism *moderately* plausible. Overall, the Committee considers the existence of a causal relation between parental marijuana smoking and AML **uncertain**, and a causal relation between parental marijuana smoking and ALL **unknown**.

Recommendations

Targeted epidemiological studies would be helpful in obtaining more information. Considering the toxic properties of cannabinol and the parallels with tobacco smoking, parents should be urgently advised to stop or avoid using cannabis at least three months before intending to conceive a child, to be continued during pregnancy and childhood.

6.7 Parental alcohol consumption

Given that the metabolites of alcohol are carcinogenic and that leukaemia can arise prenatally, parental alcohol consumption was studied as a potential risk factor for the development of childhood leukaemia in the offspring.

Evidence

A review identified in the CCG Evidence Summary studied the effect of amount, type and period of parental alcohol consumption on the incidence of childhood ALL and AML.[202] Maternal alcohol consumption one year before pregnancy showed a non-significantly higher risk for ALL in one individual study. For maternal alcohol consumption one month prior to pregnancy a significant higher risk for AML was found in one study, while for paternal alcohol consumption in several studies non-significantly higher risks for both ALL and AML were found.

On the basis of available in vitro studies, animal experiments and studies in non-pregnant women the possibility cannot be ruled out that exposure to even very low amounts of ethanol may increase the risk of cancer.[20]

IARC classifies the consumption of alcoholic beverages as ‘carcinogenic to humans’.[178]

Evaluation

Although there are indications that parental alcohol use preceding conception and maternal alcohol use during pregnancy may increase the risk of a child developing leukaemia, the Committee concludes that there is *inadequate* epidemiological evidence for an association of this kind. Since IARC has classified the consumption of alcoholic beverages as ‘carcinogenic to humans’, the Committee considers the biological plausibility as *high*. Overall, the Committee considers a causal relation between parental alcohol consumption and childhood leukaemia **possible**.

Recommendations

Since alcohol consumption is considered 'carcinogenic to humans', and parental (mainly maternal) alcohol use prior to conception and during pregnancy increases the risk of other disorders in embryos, foetuses and children (reduced fertility, miscarriage, foetal death, intra-uterine death, premature birth, congenital malformations or adverse effects on the child's psychomotor development), the Committee recommends that parents-to-be abstain from alcohol consumption prior to intended conception, and mothers also during pregnancy.[203,204]

6.8 Maternal cured meat intake

Since transplacental exposure to N-nitroso compounds have been shown to produce tumors in laboratory animals and these compounds are sometimes found in cured meat or may be formed endogenously, consumption of cured meat during pregnancy was studied as a potential risk factor for the development of cancers in the offspring.[205]

Evidence

Three of the epidemiological studies identified in a systematic review of childhood leukaemia in general, have studied the association between the intake of individual cured meats, such as luncheon meat, ham, bacon, sausages or hot dogs and childhood leukaemias.[205] Both higher and lower risks were found, but they were either non-significant or without the significance level mentioned.

Experimental investigations have shown that transplacental exposure to N-nitroso compounds, which are sometimes found in (nitrite-) cured meats, can produce tumors in laboratory animals.[205] IARC classifies the consumption of nitrite under conditions that result in endogenous nitrosation (high acidity environment of the stomach) as 'probably carcinogenic to humans'.[178]

Evaluation

There is *inadequate* evidence that consumption of cured meat is a potential cause of childhood leukaemia.[205] The experimental evidence indicates a *moderate* plausibility of causality. Overall, the Committee considers a causal relation between consumption of cured meat during pregnancy and childhood leukaemia to be **uncertain**.

Recommendations

Since IARC classifies the consumption of nitrite as 'probably carcinogenic to humans', and nitrite is used in the curing of some types of meat, the Committee

recommends targeted studies into a relation between cured meat ingestion during pregnancy and childhood leukaemia. The Committee also recommends limiting the intake of nitrite-cured meat (e.g. ham, bacon and sausages) by pregnant women.

6.9 Other chemicals

There are many chemicals for which limited or no information on health risks is available. Some of these may contribute to the risk of childhood leukaemia, such as persistent organic pollutants (POPs).[206] The 4th WHO-coordinated survey of human milk for POPs has indicated that most organochlorinated pesticides banned 25-30 years ago were below or around detection limits in Belgian human milk samples, although DDE was still found at low levels in all samples.[207] Over the last five years the levels of marker PCBs* and PCDD/Fs** in Belgian human milk decreased by 58% and 39% respectively.

Evidence

Parental occupational exposure to different chemicals and industrial dusts or fumes was assessed in three German case-control studies that were conducted from 1992-1997. Maternal exposure to paints or lacquers before conception and during the pregnancy was shown to be related to an increased risk of childhood ALL.[183]

In a large case-control study in the US an association between self-reported paternal exposure to plastic materials during the preconception period and ALL was found.[182] Also maternal exposure to plastic materials during the postnatal period were related to an increased risk of childhood ALL. An earlier case-control study in the US investigated occupational exposures of parents of 204 children (younger than 18 years) with acute non-lymphoid leukaemia. The most consistent finding was an association with pesticide exposure (see 6.1).[181] Other occupational exposures were also reported significantly more often: paternal exposure to solvents, petroleum products, plastics or lead, and maternal exposure to paints and pigments, metal dusts and sawdust.

In a nationwide case-control study in the Netherlands mothers of children with ALL reported a greater occupational exposure to chemicals (paint, petroleum products and unspecified chemicals) during pregnancy than mothers of controls.[208]

Among 837 children with ALL studied by the Childrens Cancer Study Group in the United States, 15.2% showed *ras* mutations.[184] Specific *ras* mutations in the leukaemic cells were found to be associated with parental exposure to certain

* PCBs: polychlorinated biphenyls.
** PCDD: polychlorinated dibenzo-p-dioxin; PCDF: polychlorinated dibenzofuran.

medications, solvents, plastic materials, oil, coal products and other hydrocarbons. However, the risk of childhood leukaemia is modified by genetic characteristics affecting the metabolic activation or inactivation of exogenous chemicals. The risk for ALL increased threefold when three susceptibility genotypes occurred in the same children.[209] This may suggest a causal relation between environmental exposures, specific *ras* mutations and ALL.

PCBs, which were classified as 'probable human carcinogens' by IARC in 1987[178] and which cause perturbations of the immune system, may represent a previously unrecognised risk factor for childhood leukaemia.[210] In a case-control study in the USA, the highest levels of PCBs in carpet dust were associated with a three times higher risk of ALL.

Other substances that could potentially contribute to an increased risk of childhood leukaemia include specific phthalates (plasticisers); di(2-ethylhexyl)phthalate is classified by IARC as a 'possible human carcinogen.[178]

Evaluation

Epidemiological and biological data provide, respectively, limited and moderate to high evidence that specific (classes of) reactive (mutagenic or receptor-binding) chemical agents found in the environment might, either alone or in combination with other factors, be contributing to childhood leukaemia. The Committee considers a causal relation for PCBs **likely**, for plasticisers **possible** and for other chemicals **unknown**.

Public health relevance

Children that carry genetic polymorphisms which result in a comparative inability to process chemicals to which they are environmentally exposed, show a higher incidence of leukaemia.[207] This indicates that these chemicals play an important role in the causation of leukaemia and that a segment of the population is at increased risk of leukaemia from these chemicals. This might explain a sizeable fraction of childhood leukaemia.[211] However, specific information is not available.

Recommendations

Many chemicals may, either alone or in combination with other factors, contribute to the induction or development of childhood leukaemia. This requires an integrated approach. Since many different mutagenic or receptor-binding agents may be involved in the development of leukaemia, it seems desirable and reasonable to complement the traditional anti-microbial hygiene with 'physical-chemical hygiene', limiting environmental exposures to possibly harmful agents as much as feasible.

Furthermore, targeted epidemiological studies should be performed on agents associated with an increase in chromosomal abnormalities or DNA abnormalities (gene mutations) in human blood cells, as these agents have access to and are active in human haematopoietic tissues. These studies should not only target pesticides and organic solvents, but also other potentially reactive or genotoxic chemicals, such as polychlorinated biphenyls (PCBs) and phthalates (plasticisers).

7 Biological and other factors

This chapter explores the available evidence on the role of a number of other environmental factors on the occurrence of childhood leukaemia: infectious agents and immune reactions, maternal folate and vitamin supplementation, birth weight and socio-economic status. Some of these may have a protective effect.

7.1 Infections and immune reactions

The relationships between various forms of immunological stimulation and the occurrence of childhood cancer are diverse and complex. In some cases a protective effect may be involved. In the following sections the Committee discusses the available scientific evidence regarding four groups of indicators for infections and immune reactions which have been identified as possible influences on childhood leukaemia: infectious exposures, early social contacts, allergies and breast-feeding.

These possible associations may also shed light on an underlying mechanism. In this regard, Greaves has proposed a general 'delayed-infection' hypothesis for childhood leukaemia[36], in which the absence or diminution of infections early in life is stated to predispose the immune system to abnormal responses ('inadequate priming') when exposure to common infectious agents occurs at a later stage in life. A deregulated immune response to infection could then result in a potent inflammatory response.

Postnatal malignant progression of prenatally initiated preleukaemic clones may also play a role in the risk of ALL, particularly common B-cell precursor ALL (cALL), the most common type of ALL. In other words, children who face a narrower range of antigens in early childhood may be, according to Greaves, more susceptible to leukaemogenesis in their maturing B-cell compartment.

7.1.1 Infectious exposures

There are two hypotheses concerning the role of infections in the aetiology of childhood leukaemia, each relating to a specific time of exposure:[212]

- Absence or diminution of infections early in life, later followed by exposure to common infections (Greaves' hypothesis).
- Unusual infectious exposures, due to unusual 'population mixing' (Kinlen's hypothesis).

Evidence

In a review identified in the CCG Evidence Summary, different infectious exposures were shown to be associated with, on the one hand, direct indicators of exposure to infectious agents, and to be associated with, on the other hand, indirect ('proxy') indicators, such as vaccinations, breast-feeding, early day-care attendance and unusual 'population mixing'.[212] Where maternal infections during pregnancy are concerned, several studies have shown significantly or non-significantly higher risks for ALL. In the case of childhood infections, vaccinations and 'individual social mixing' (birth order), inconsistent results (i.e. both significantly higher and lower risks in identical settings and groups) were found. One study identified a statistically significant association between paternal occupational contact levels (i.e. the number of social contacts with the father whilst at work) and a higher risk for ALL.

For childhood leukaemia in general two individual studies showed inconsistent results with respect to a relation between paternal occupational contact levels and childhood leukaemia.[213] Also for maternal infections, childhood infections, different vaccinations and birth order, inconsistent results were found.

According to the 'population mixing' hypothesis of Kinlen, large increases or shifts in population enhance the opportunity to infect members of the resident population with infectious agents for which the community's children have developed limited immunity.[214] Kinlen has suggested that an epidemic of an underlying infection, to which childhood leukaemia may be a rare response, is promoted by marked population mixing in rural areas, where the prevalence of susceptible individuals is higher than average.

Although the working mechanisms still need to be determined, a possible aetiological mechanism may be found in an abnormal immune response to common infections.[36] This idea is supported by several discoveries: the retrovirus human T-cell lymphotropic virus 1 (HTLV1) is a causative factor for adult T-cell leukaemia and lymphoma; leukaemia in domestic cattle, cats and chickens is viral in origin; and Epstein-Barr virus is the causative agent in some lymphomas. Evidence from the mechanisms in other haematological cancers also supports this view.

Evaluation

The epidemiological evidence shows inconsistent results, and does not sufficiently support the hypotheses of Greaves and Kinlen to draw any conclusions as to their accuracy. The Committee therefore concludes that there is *inadequate* evidence that (responses to) different infectious exposures are associated with an increased risk of childhood leukaemia. One of the reasons for these complex findings may be that the patterns of exposure, the timing of

infections and the immunological response are associated with multifactorial determinants.[36] In addition, the Committee does not rule out that other than infectious environmental factors may play a role in explaining the observed association with population mixing. Large increases in a population (i.e. forming of 'new towns') might, for instance, also be associated with exposures to solvents in new buildings.

Because of the delayed-infection hypothesis of Greaves, the Committee considers the biological plausibility as *moderate*. The Committee therefore considers a causal relation between different infectious exposures and the incidence of ALL and childhood leukaemia in general **uncertain,** and considers the existence of a relation between infectious exposures and AML **unknown**. It may be possible that childhood exposures to common infections offer some protection against childhood leukaemia, specifically against ALL. Parental or childhood exposures to specific infectious agents (e.g. Epstein-Barr virus) may, however, increase the risk.

Recommendations

Since there is a lack of adequate data on a possible relation between infectious exposures and childhood leukaemia, more research in this area is warranted. It would be especially useful if, in addition to infectious agents, other environmental determinants of population mixing would be investigated.

7.1.2 Early social contacts

A rare response to common infections acquired by personal contact with infected individuals may be another relevant environmental factor in developing childhood leukaemia.[215] This has been studied by looking into a possible association between day-care attendance and other early social contacts and the risk of childhood ALL, with specific attention paid to early-life exposure to infections and any protection this may provide against ALL.

Evidence

In a review in the CCG Evidence Summary, the association between duration and timing of day-care attendance early in life (less than two years of age) and childhood ALL was investigated.[215] This exposure measure served as an indicator for the increased likelihood of early exposure to infections. A pooled analysis of the identified data showed a significantly lower risk for common-ALL*.

* Most frequent type of ALL: common B-cell precursor ALL (cALL).

Evaluation

The epidemiological data provide sufficient evidence to suggest a protective association between early social contacts and the risk of ALL.[215] Because of the 'delayed-infection' hypothesis of Greaves, the Committee considers the biological plausibility as *moderate*. A protective effect of early social contacts in the case of ALL is therefore considered **likely**. In the case of AML it is **unknown** whether such an effect occurs.

Public health relevance

No information is available on population attributable fractions. However, in view of the widespread nature of early social contacts, the Committee considers their potential protective effect to be very important.

Recommendations

The Committee considers further research into the possible protective effects of early social contacts not of high priority. The Committee does however recommend to stimulate early social contacts between young children. This will also be beneficial for reasons other than reducing the risk of childhood leukaemia.

7.1.3 Allergies

Higher incidences of both childhood leukaemia and allergic diseases are found in western industrialised countries, as compared to developing countries.[216] Worldwide incidence data indicate a significant correspondence between rates of childhood allergies and ALL, suggesting there may well be shared infectious or immunological risk factors.[36] A decline in exposure to infections in early childhood might play a role in the aetiology and increase of both.

Evidence

In a systematic review identified in the CCG Evidence Summary, pooled analyses showed a significantly lower risk for ALL in persons with hay fever, eczema and overall allergy.[216]

Evaluation

In spite of the above mentioned correspondence between childhood allergies and ALL in 'ecological' studies, from case-control studies, there is *sufficient* evidence to suggest an inverse association between allergy and the risk of

ALL.[216] However, the Committee considers the biological plausibility of a causal relation between allergy and childhood leukaemia as *low*. The Committee therefore considers a protective effect of allergy (i.e. an allergic constitution) for ALL **possible** and for AML **unknown**.

Public health relevance

Despite the frequent occurrence of allergies in the population*, there is no information available to derive population attributable fractions.

Recommendations

The Committee sees no reason to give priority to further studies in this area.

7.1.4 Breast-feeding

It has been suggested that breast milk may play a role in the prevention of certain childhood cancers.[217]

Evidence

In the systematic review retrieved in the CCG Evidence Summary, breast-feeding was associated with a significantly lower risk for ALL and AML.[217]

Given the multiple immunological effects of breast-feeding in offspring, Greaves has considered this relation to be biologically plausible.[218]

Evaluation

There is *sufficient* evidence that breast-feeding is inversely associated with the development of childhood leukaemia. The Committee considers this to be *moderately* biologically plausible.[218] The Committee therefore considers an inverse causal relation between breast-feeding and AML and ALL **likely**.

Recommendations

Since the Committee has concluded that a protective effect of breast-feeding is likely, and bearing in mind that breast-feeding has many other benefits, the Committee supports the recommendation made by the Netherlands Nutrition Centre, which is in turn based on the recommendations by the WHO, that, whenever feasible, infants should be exclusively breast-fed up to the age of approximately six months.[219,220]

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* In the Netherlands, at least one in four children (12-14 years) reported allergic disorders.[200]

7.1.5 Overall conclusion and recommendations

Whether other forms of immunological stimulation have the same protective effect as early social contacts, allergies and breast-feeding is not clear.[215] The observed complexity certainly reflects the complexity of the stimulating and inhibiting influences of different immunological stimuli on the proliferation of the various cell types in haematological and immunological tissues. Because of the unknown interactions of infectious diseases, allergies and social contacts, the Committee concludes that there is limited evidence that infections and immune reactions are associated with the risk of childhood leukaemia.

The Committee therefore considers a protective effect of exposure to common childhood infections and immune reactions regarding childhood leukaemia, and specifically regarding ALL, to be **possible**. Parental or childhood exposures to specific infectious agents (e.g. Epstein-Barr virus) may, however, increase the risk of childhood leukaemia.

The Committee concludes that not enough knowledge currently exists to recommend measures to prevent or stimulate exposure to infections or other immune reactions. An exception is made in the case of breast-feeding, since a recommendation in this regard is in line with existing advice to mothers. To further understand the role of infections or other immune reactions, more research would be necessary, for instance to explain space-time clustering of the incidence of childhood leukaemia in different populations.

7.2 Maternal folate and vitamin supplementation

Given the hypothesis that deficiencies in vitamins and some other micronutrients might increase the risk of cancer, and that leukaemia can arise prenatally, maternal folate and vitamin supplementation were studied as potential protective factors in the development of childhood leukaemia in the offspring.[221]

Evidence

A review discussed in the CCG Evidence Summary studied the association between maternal use (and dose) of folic acid and other vitamin supplements before and during pregnancy, and the risk of ALL.[221] In one study, a non-significantly higher risk for ALL was observed in relation to folate supplementation before pregnancy. Pooled analyses showed non-significant results in the case of vitamin supplementation before pregnancy. For vitamin supplementation during pregnancy, however, a significantly lower risk for ALL was observed. Combinations of vitamins and folate did not reveal any associations.

A protective effect of maternal folate supplementation during pregnancy against the occurrence of childhood leukaemia is biologically plausible, given its dual roles in methylation and the synthesis and repair of DNA.[221]

Evaluation

There is *limited* evidence that extra vitamin supplementation during pregnancy protects against ALL.[221] However, the Committee found no evidence to consider this plausible and therefore considers a causal relation between vitamin supplementation during pregnancy and a decrease in ALL **uncertain**. Although the Committee considers a causal relation with folate intake as *moderately* plausible, there is *inadequate* evidence from epidemiological studies that the intake of folate before or during pregnancy has a protective effect. So, whether a protective relation with folate supplementation exists is also **uncertain**. Based on the CCG Evidence Summary a causal relation with AML is **unknown**.

Recommendations

More research is required to obtain insight in the possible protective effect of vitamin supplementation during pregnancy on the risk of childhood leukaemia, in particular ALL. For other reasons than reducing the risk of childhood leukaemia, and since it is relatively easy to accomplish, folate supplementation should be promoted from four weeks before intended conception until eight weeks after conception.

7.3 Birth weight

A growing body of evidence suggests that childhood leukaemia may be initiated in utero when lymphoid and myeloid cells are not fully differentiated and are particularly susceptible to malignant transformation.[222] Likewise, stem cells that give rise to the myeloid cell line may also be susceptible to circulating growth factors and hormones. These then act to increase the size of the stem cell pool, which in turn increases the total number of replicating cells now at risk for conversion into tumour cells. This subsequently may increase the risk of leukaemia. Since one factor related to the size of the stem cell pool is birth weight, this has been postulated as a risk factor for childhood leukaemia. However, birth weight has also been associated with other factors, some of which have been discussed before, e.g. smoking

Evidence

In the relevant review identified in the CCG Evidence Summary, a high birth weight was associated with a higher risk of ALL and AML, and a low birth

weight with a higher risk of AML.[222] Furthermore, for each kilogram increase in birth weight a higher risk for ALL was found.

Evaluation

There is *limited* evidence that birth weight, affecting many physiological parameters, is associated with the risk of ALL (higher birth weight) and AML (higher and lower birth weight).[222] The Committee considers the biological plausibility of a relation between a high birth weight and childhood leukaemia to be *moderate*. The plausibility that a relation with low birth weight exists is considered *low*. The Committee therefore considers a causal relation between a high birth weight and ALL or AML **possible**, and one between a low birth weight and AML **uncertain** and for ALL **unknown**.

Recommendations

In view of the benefits for many other aspects of health, a normal birth weight should be aimed for during pregnancy.

7.4 Socio-economic status

A long-held view links higher socio-economic status (SES) to higher rates of childhood leukaemia.[223] Some recent studies, however, showed associations in the opposite direction.

Evidence

In a review identified in the CCG Evidence Summary, associations were studied between childhood ALL and AML and socio-economic circumstances.[223] Family income and mother's education showed inconsistent associations with ALL, with significantly higher AML rates, however, being found when family income was lower. In the case of paternal education, (non-)significantly higher ALL rates were associated with higher SES, while (non-)significantly higher AML rates once again showed an association with lower SES. One study, however, found significantly higher ALL rates to be related to 'ecological' SES measures at an aggregated or population level, i.c. higher education and occupational class. For childhood leukaemia in general, inconsistent associations were found for family income, parental education, father's occupational class and household density.[223]

The authors of the original review concluded that case-control studies conducted in North America since 1980 have consistently reported inverse (negative) associations of childhood leukaemia with individual measures of family income, mother's education and father's education.[223] In contrast, the

incidence of childhood leukaemia has consistently shown to be lower when father's occupational class is identified as low.

Evaluation

The systematic analyses provide inconsistent evidence, showing both positive and negative associations of childhood leukaemia with indicators of SES. However, SES might only be a proxy for other factors that might explain the (indirect) relations. Based on these results, the Committee considers there to be *inadequate* epidemiological evidence for such associations. The Committee also considers the biological plausibility that a causal relation exists to be *low*. According to the Committee, the existence of a causal relation between SES and childhood leukaemia is therefore **unknown**.

8 Conclusion

The main objective in this report has been to evaluate the existing scientific evidence on possible relations between environmental factors and the occurrence of childhood leukaemia, and to recommend balanced measures to reduce risks when sufficient knowledge is available or uncertainties exist. In this final chapter, the Committee gives an overview of its conclusions and recommendations.

8.1 Conclusions on possible associations

Given that leukaemia is the most common malignancy in children, and observing the increase that has occurred in the last decade of the 20th century, there is every reason to look for ways to reduce environmental risks, although this trend now seems to have stopped and has maybe even been reversed. It needs to be noted, however, that a certain level of incidence of childhood leukaemia is inevitable, since genetic susceptibilities, naturally occurring exposures and man-made factors all play a role. Separating these influences to arrive at a baseline or 'natural' occurrence of childhood leukaemia is impossible, since the development of leukaemia is a multifactorial process, depending on multiple consecutive events, and with simultaneous exposure to multiple factors.

Complicated interplay of factors

The most important conclusions therefore are that (a) the majority of leukaemia cases cannot be explained; (b) only a small fraction of leukaemia cases might be prevented. Consequently, suggesting a full range of measures aiming at a baseline incidence is not possible. Where sufficient evidence is available for associations with individual factors and uncertainties exist regarding the complex interplay of risk factors, the precautionary principle can be used as a guideline. The uncertainties are due to our rudimentary knowledge about the multistep process that leads to the disease and about the way environmental factors, such as exposure to pesticides or other chemicals, affects this process. Knowledge about the role of concurrent or subsequent exposures and about critical pre- and postnatal periods of susceptibility is lacking or in varying degrees deficient.

Likelihood of causality per factor

Arriving at conclusions on the role of separate causal relations has not proved to be easy. Most possible relations under consideration in this report could not be sufficiently established, given the available epidemiological and experimental evidence.

In the following two tables the Committee summarises the findings, indicating for each factor to which extent the available evidence supports the likelihood of an association with childhood leukaemia and what measures and research are proposed. Table 6 contains the conclusions on possible risk factors, whereas Table 7 summarises the findings on factors with a possibly protective influence. Whenever a distinction could be made between ALL and AML this is indicated. In all other cases the Committee refers to 'childhood leukaemia'.

For most risk factors it has not been possible to calculate which percentage of leukaemias they cause. In a few cases, the Committee was able to provide rough estimates of 'population attributable risks' (PAFs), ranging from less than 1% for exposure to magnetic fields from overhead power lines up to 15-20% for exposure to naturally occurring ionising radiation. Since these numbers are very uncertain, they are not provided in the table.

8.2 Recommended measures

Which measures could be taken to reduce the impact of environmental factors on childhood leukaemia, or to utilise protective influences? Since many different mutagenic or receptor-binding agents may be involved in the development of leukaemia, it seems desirable and reasonable to complement the traditional anti-microbial hygiene with 'physical-chemical hygiene', limiting environmental exposures to potential reactive agents as much as feasible.

Limited array of measures

In theory, the expected contribution to the number of cases of childhood leukaemia would be an important consideration in selecting the most promising measures. It was shown in the previous chapters, however, that for most factors no reliable estimate could be made. Moreover, in most cases not even the relationship itself has been scientifically proven.

Only where ionising radiation is concerned a causal relationship has been established. For benzene and paternal tobacco smoking such a relation is deemed to be likely, for pesticides it is considered possible to likely, while early social contacts and breast-feeding are likely protective factors. In all other cases, less certainty exists on the possible relation between an environmental influence and

Table 6. The likelihood of involvement of environmental risk factors in the causation of childhood leukaemia.

Environmental factor	Potential exposure	Type of leukaemia (when differentiated)	Likelihood of causality	Proposed measures	Proposed research
Ionising radiation	Ionising radiation	Childhood leukaemia	Established	Exposure reduction (ALARA)	Assessment of exposure of unborn children and infants. Biological effects of pre- and postnatal diagnostic X-rays (esp. CT scans)
Electromagnetic fields	Extremely Low Frequency magnetic fields	Childhood leukaemia	Possible	Exposure reduction	
		ALL	Possible	Exposure reduction	
		AML	Unknown		
	Radiofrequency radiation	Childhood leukaemia	Unknown		Monitoring actual exposures
Ultrasound	Diagnostic ultrasound scans	Childhood leukaemia		Optimisation and standardisation	Effects of more intensive or frequent ultrasound scans
	- routine/limited		Unlikely		
	- frequent/intensive		Unknown		
Chemicals	Pesticides	Childhood leukaemia	Possible to likely	Preconceptional counselling to reduce exposure	Monitoring exposures among occupationally exposed women
		ALL	Possible to likely	Preconceptional counselling to reduce exposure	Monitoring exposures among occupationally exposed women
		AML	Uncertain to possible	Preconceptional counselling to reduce exposure	Monitoring exposures among occupationally exposed women
	Benzene	Childhood leukaemia	Likely	Preconceptional counselling to reduce exposure	Monitoring exposures in specific situations
	Formaldehyde	Childhood leukaemia	Possible	Exposure reduction	
	Styrene	Childhood leukaemia	Uncertain	Exposure reduction	
	Other organic solvents	Childhood leukaemia	Unknown	Exposure reduction	Epidemiological and experimental studies for commonly encountered organic solvents

Environmental factor	Potential exposure	Type of leukaemia (when differentiated)	Likelihood of causality	Proposed measures	Proposed research
	Inorganic arsenic in drinking water	Childhood leukaemia	Possible	Exposure reduction	
	Paternal tobacco smoking	Childhood leukaemia	Likely	Refrain from tobacco smoking	
	Maternal tobacco smoking	Childhood leukaemia	Possible	Refrain from tobacco smoking	
	Parental marijuana smoking	AML	Uncertain	Refrain from marijuana smoking	Epidemiological studies
		ALL	Unknown	Refrain from marijuana smoking	Epidemiological studies
	Parental alcohol consumption	Childhood leukaemia	Possible	Refrain from alcohol consumption	
	Maternal cured meat intake	Childhood leukaemia	Uncertain	Exposure reduction	Effects of cured meat ingestion during pregnancy
	PCBs	Childhood leukaemia	Likely	Preconceptional counselling to reduce exposure	Epidemiological studies
	Plasticisers	Childhood leukaemia	Possible	Preconceptional counselling to reduce exposure	Epidemiological studies
	Other chemicals	Childhood leukaemia	Unknown	Exposure reduction	Epidemiological studies on agents associated with DNA damage
Biological and other factors	Infectious exposures	Childhood leukaemia	Uncertain		More research in this area
		ALL	Uncertain		
		AML	Uncertain		
	High birth weight	ALL	Possible		
		AML	Possible		
	Low birth weight	ALL	Unknown		
		AML	Uncertain		
	Socio-economic status	Childhood leukaemia	Unknown		

Table 7. The likelihood of a protective influence of environmental factors in the occurrence of childhood leukaemia.

Environmental factor	Potential exposure	Type of leukaemia (when differentiated)	Likelihood of causality	Proposed measures	Proposed research
Biological and other factors	Early social contacts	ALL	Likely	Encourage	
		AML	Unknown	Encourage	
	Allergies	ALL	Possible		
		AML	Unknown		
	Breast-feeding	ALL	Likely	Encourage	
		AML	Likely	Encourage	
	Maternal vitamin supplementation during pregnancy	ALL	Uncertain		More research on protective effect of vitamin supplementation during pregnancy
		AML	Unknown		
	Maternal folate supplementation	ALL	Uncertain	Encourage	
		AML	Unknown	Encourage	

childhood leukaemia, ranging from 'possible' in a number of cases to 'uncertain' or 'unknown' in others.

Another problem is that not every environmental factor can be influenced by policy measures. Cosmic radiation, for instance, is not something for which measures are practically available, except in the case of flying personnel during pregnancy.

Still, several options present themselves when aiming for a reduction in the occurrence of childhood leukaemia. If avoiding exposures that are suspected to contribute to childhood leukaemia is a reasonable option, this should be contemplated, especially if measures to this effect could also protect against other adverse health effects.

The situation with childhood leukaemia is characterised by uncertainty, complexity and ambiguity. Therefore it is warranted to take, as the Committee has done, a precautionary perspective to guide the risk assessment and subsequent risk management.

The Committee suggests preventive measures when (a) plausible and relevant environmental risk factors of childhood leukaemia have been identified or (b) behavioural risk factors have been identified that are in line with existing recommendations given for other reasons, e.g. smoking and alcohol consumption during pregnancy.

Three measures stand out because of their possible contribution to decreasing the number of cases of childhood leukaemia: reducing exposure of parents and children to ionising radiation, especially through medical applications; reducing

occupational and residential exposure to pesticides and to benzene; and reducing parental tobacco smoking, also to reduce the risk of several other adverse health effects. Although considerable uncertainty still exists, the Committee considers it very likely that the contribution of these factors to the incidence of childhood leukaemia in high-risk groups might be substantial.

Reducing exposure to radiation

Medical radiation. Limiting the exposure to ionising radiation for medical purposes is important for both women in their (early) pregnancy and for children. In applying medical radiation, the risks always have to be justified and weighed against the advantages, but this is especially important where these two groups are concerned. The Committee feels that risk awareness in physicians can be improved.

Applying optimisation and diagnostic reference levels is the way to achieve exposure reduction. Whenever possible, diagnostic techniques that do not involve ionising radiation should be used, such as ultrasound. However, this technique should also be used prudently: although a causal relation with limited exposures to routine ultrasound scans is considered unlikely, ultrasound scans should not be offered without medical indication. The Committee therefore sees a need for stricter justification standards and optimisation procedures for ultrasounds as well.

Other radiation sources. Where other radiation sources are concerned, the focus should also be on the reduction of exposure to as low as reasonably achievable (ALARA). This applies, for instance, to the emission of radioactive noble gases from nuclear facilities. These emissions should be monitored.

Reducing exposure to chemicals

Pesticides. Although uncertainty exists about the risks of occupational and residential use of pesticides, a reduction in the use of pesticides should be considered a priority. When using pesticides at home (i.e. biocides for pest control), risks and benefits should be carefully weighed. Especially women who want to become pregnant or who are already expecting should refrain from using pesticides, or should make sure they use extra protection measures.

Other chemicals. The available evidence warrants taking measures to limit or prevent exposure of children and pregnant women to benzene and specific classes of other chemicals, such as PCBs.

Reducing other environmental risks

Reducing environmental exposure to ELF magnetic fields, radon and chemicals. Precautionary measures are most obviously required for environmental factors that may possibly contribute to childhood leukaemia. Examples are limiting exposures to ELF magnetic fields from high-voltage power lines and, mainly for reasons other than childhood leukaemia, striving for a further reduction in exposures to radon from soil and building materials, as well as to specific chemicals such as formaldehyde, inorganic arsenic and plasticisers.

Avoiding parental smoking and consumption of alcohol and cured meat. For several parental lifestyle factors that have been linked with other diseases, considerable uncertainty exists where a causal relationship with childhood leukaemia is concerned. This applies to tobacco and marijuana smoking as well as to alcohol use. In these cases, a possible risk of leukaemia for the unborn child could provide an extra incentive to refrain from smoking and alcohol consumption when the conception of a child is intended. Although uncertainty exists about the evidence for a causal relation between parental intake of cured meat and childhood leukaemia, the Committee nevertheless recommends limiting the intake of nitrite-cured meat (e.g. ham, bacon and sausages) by pregnant women.

Enhancing protective influences

Encouraging folic acid supplementation and breast-feeding. Some of the factors the Committee has studied may protect against childhood leukaemia, although once again considerable uncertainty exists. Folate supplementation before the intended conception and during early pregnancy is already recommended because of other beneficial effects, but may also reduce the risk of childhood leukaemia. The Committee therefore strongly supports this recommendation. The Committee also recommends to breastfeed children up to the age of approximately six months, whenever feasible, in line with the general recommendation.

The importance of risk communication and public participation

Risk communication is the exchange of information and opinions between the authorities, the public and other parties involved, about the nature and extent of a risk.[224] The message should be tailored to the needs of the receiver and must include clear information on what is known about the plausibility of potential health risks and the certain and uncertain effects of preventive measures. Different value judgements should be taken into account, and the risk communication should contribute to a balanced risk awareness. This can help

people make informed choices. Any risk communication should also clarify that at a population level many factors may be shown to have an impact and that there is a complex interplay of causes; it will therefore never be possible to explain individual cases of leukaemia.

As an important part of risk communication, the Committee recommends that women of childbearing age should be counselled, in order to create awareness of the risk of certain potentially harmful environmental and lifestyle factors previous to an intended conception.

Risk communication targeted at the general public or professionals can only be part of the approach. For medical radiation, risk awareness created by a risk communication programme can be a driving force in adopting new protocols and increasing the willingness to reduce exposure. Besides, implementation of measures is necessary, not only to reduce exposure to medical radiation, but also to radon, ELF magnetic fields and pesticides.

In conclusion, a number of factors discussed in this report have been shown to contribute to the risk of childhood leukaemia, or are likely to do so. Other factors carry only a small risk, or may turn out to be not involved at all. Despite this, people may worry, particularly in relation to locally observed clusters of childhood leukaemia, for instance around high voltage power lines. When concerns are raised, proper risk communication can help ensure that those involved are able to arrive at an informed opinion about risks that may be posed by local environmental factors. The involvement of residents at an early stage of risk assessment and risk management is a precondition for an effective policy to address local environmental health concerns or concerns of specific groups. Openness and transparency are key principles in this process.

8.3 Research needs

In identifying research needs, the expected contribution of a factor to the number of cases of childhood leukaemia should be the most important consideration, with exposure at the population level as the guiding principle. This means that studies need to focus on factors to which a large number of people are exposed or factors which greatly impact a smaller group. However, other considerations can play a role as well.

On the incidence of childhood leukaemia

Because of the relatively small numbers of childhood leukaemia cases per country, there is a need for international collaboration in studying variations in incidence in relation to variations in environmental exposures.

There is also a need for further research into why the peak in incidence occurs early in life. This might be associated with exposures during critical periods of differentiation.

On genetic factors

Although insight into the genetic susceptibility of childhood leukaemia to risk factors is emerging, the interaction with environmental factors remains to be explored. A research question closely associated with that in the previous section concerns the causes that may explain the peak in incidence occurring early in life for genetic subtypes of ALL.

On environmental risk factors

In epidemiological research designs, the Committee recommends to pay more attention to the quality of exposure assessment and to specific leukaemia diagnoses (ALL/AML). In the analyses, specific attention needs to be paid to the most relevant exposure periods: before and during pregnancy, and in early childhood. Because of the differences in potential damage, it is important to differentiate, in research regarding the critical time windows of exposure during pregnancy, in 'early' (first 3-6 weeks), 'mid' and 'late' (last trimester).

On combined exposures

Children and their parents are exposed to mixtures of different agents. However, hardly any study has looked into interactions, for instance between prenatal parental and postnatal environmental exposures. Therefore, the Committee recommends that, in epidemiological studies, more attention should be paid to the accumulation of risks of combined exposures.

On ionising radiation

A lot is known about the mechanism underlying the relation between leukaemia in children and the exposure to ionising radiation, but more research is still needed concerning the role of a number of specific exposure situations. Life has evolved under continuous exposure to natural ionising radiation, but due to the concentration of radioactive substances in building materials and high-altitude flights, and especially due to medical radiation, exposures have increased. More research into these types of exposures is therefore needed.

Medical radiation. More detailed and precise data should be acquired on the exposure of unborn children and infants, including subgroups such as prematurely born children, in order to better apply justification of exposure and to apply dose reduction strategies for X-ray examinations. In addition, research is needed into the biological effects of pre- and postnatal diagnostic X-ray exposure in general and exposures from CT scans in particular.

Residential proximity to nuclear installations. The Committee recommends to monitor the emissions of radioactive noble gases from nuclear installations, and to study locations that differ in the way emissions of radioactive noble gases are handled and locations in which accidental releases of radioactive noble gases have occurred. Also, it may be helpful to pool epidemiological data on all potential risk factors (i.e. not only those concerning ionising radiation) related to the vicinity of nuclear power plants on an international scale.

Nuclear accidents. More research is also needed on the health effects, including non-cancer effects, of chronic internal exposures of children resulting from environmental contamination by radionuclides released during a nuclear accident.

On ultrasound scans

Ultrasound scans are offered to all pregnant women in the first and second trimester of pregnancy and are generally regarded as safe to the foetus. Current ultrasound technology, however, has a significantly higher output potential than the older machines used in most clinical studies. Ultrasound investigations during pregnancy are also commercially provided for non-medical purposes. More knowledge about the possible adverse effects of intensive and/or frequent ultrasound scans (e.g. following in vitro fertilisation, IVF) on leukaemia and other diseases is therefore needed.

On electromagnetic fields

More experimental research into possible carcinogenic mechanisms of extremely low frequency and radiofrequency electromagnetic fields is recommended.

On pesticides and other chemicals

The uncertainty about the leukaemic potential of different chemical environmental factors is large. So it is important to gain more insight into the possible contribution of separate factors to the occurrence of childhood leukaemia.

Pesticides. The Committee recommends the monitoring of pesticide exposures among occupationally exposed women, at least of reproductive age, and to incorporate biomarkers of exposure in these studies, whenever feasible.

Benzene. In order to obtain more solid evidence on the causal relation between exposure to benzene and childhood leukaemia, targeted exposure monitoring studies should be performed.

Other organic solvents. There is a need for both epidemiological and experimental studies into the relation between commonly encountered organic solvents and childhood leukaemia.

Cured meat. Nitrite is used in the curing of some types of meat. Because IARC classifies the consumption of nitrite as 'probably carcinogenic to humans', the Committee recommends targeted studies into a possible relation between cured meat ingestion during pregnancy and childhood leukaemia.

Other chemicals. Many other chemicals might, either separately or in combination with other factors, contribute to childhood leukaemia. Therefore targeted epidemiological studies should be performed on agents associated with an increase in chromosomal abnormalities or DNA abnormalities (gene mutations) in human blood cells, as these agents have access to and are active in human haematopoietic tissues. These studies should not only target pesticides and organic solvents, but also other potentially reactive or genotoxic chemicals, such as polychlorinated biphenyls (PCBs) and phthalates.

On other risk factors

Since there is a lack of adequate data on a possible relation between infectious exposures and childhood leukaemia, research in this area is warranted, for instance into the space-time clustering of childhood leukaemia incidence in different populations. Finally, more research is required to obtain insight in the possible protective effect of vitamin supplementation during pregnancy on the risk for childhood leukaemia, in particular ALL.

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Annexes

A The Committee

B Consulted Experts / Reviewers

C ALL/AML CCG: Evidence Summary

D Childhood leukaemia in general: Evidence Summary

E Causality considerations and limitations

F Classifications of evidence

A The Committee

- M. van Eijkeren, Professor of Radiation Oncology, University of Ghent, Belgium, *chairman*
- F. Woudenberg, Psychologist, Public Health Service Amsterdam, The Netherlands, *vice-chairman*
- G. Eggermont, Visiting professor of Radiation Protection, Vrije Universiteit Brussel, Belgium
- J. Francart, Epidemiologist, Research Manager Belgian Cancer Registry, Brussels, Belgium, (since July 2012)
- S. van Gool, Professor of Paediatric Oncology, KU Leuven, Belgium
- W.A. Kamps, Emeritus Professor of Paediatric Oncology, University of Groningen, The Netherlands
- A. Keverling Buisman, Expert in Ionising Radiation, The Netherlands
- M. Kirsch-Volders, Professor of Genotoxicity, Vrije Universiteit Brussel, Belgium
- L.C.M. Kremer, Paediatrician, Academic Medical Centre Amsterdam, The Netherlands, and Head, International Cochrane Childhood Cancer Group
- N. van Larebeke, Professor of Carcinogenesis and Cancer Prevention, University of Ghent, Belgium
- G. van Maele-Fabry, Professor of Systematic Review and Meta-analysis, Université catholique de Louvain, Belgium
- W.F. Passchier, Emeritus Professor of Risk Analysis, Maastricht University, The Netherlands
- R. Pieters, Professor of Paediatric Oncology, Erasmus Medical Centre Rotterdam, The Netherlands
- B. Poppe, Geneticist, University of Ghent, Belgium
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- P. Smeesters, Expert in Ionising Radiation, Federal Agency for Nuclear Control, Brussels, Belgium
- L. Verschaeve, Professor of Genetic Toxicology, University of Antwerp & Scientific Public Health Institute Brussels, Belgium
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- K. Cauwerts, Veterinary Microbiologist, Superior Health Council, Brussels, Belgium, *scientific secretary* (until April 2012)
- M. Drijver, Medical Public Health Specialist in Environmental Health, Epidemiologist, Toxicologist, Health Council of the Netherlands, The Hague, The Netherlands, *scientific secretary*
- L. Peeters, Pharmaceutical Biotechnologist, Superior Health Council, Brussels, Belgium, *scientific secretary* (since April 2012)
- E. van Rongen, Radiobiologist, Health Council of the Netherlands, The Hague, The Netherlands, *scientific secretary*

During the third meeting D. Heederik, Professor of Health Risk Assessment, Institute for Risk Assessment Sciences, University Utrecht, The Netherlands, was invited to give his views on quantitative risk assessment in human observational studies.

B Consulted experts

A draft version of this report has been reviewed by members of several Standing Committees of the Health Council of the Netherlands, by members of the Council and expert groups of the Superior Health Council, by (co)authors of meta-analyses on pesticides in relation to childhood leukaemia and by members of the EuSANH network. The following experts have contributed to this process:

- P. Ambrósio, Lab. de Doenças Hematológicas Malignas, Unidade de Citogenética, Departamento de Genética, Instituto Nacional de Saúde Dr. Ricardo Jorge, Lisboa, Portugal
- A.C. Ansink, Gynaecologist-oncologist, Chief medical officer curative medicine, Health Inspectorate, Ministry of Health, Utrecht, The Netherlands
- I. de Beaufort, Professor of Medical Ethics, University Medical Center, Rotterdam, The Netherlands
- Y. Benoit, Professor of Paediatric Hemato-oncology, Ghent University Hospital, Ghent, Belgium
- H.F. Boersma, Radiation Protection Unit, University of Groningen, The Netherlands
- H.R. Büller, Professor of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
- M. Duverger van Bogaert, PH-toxicology section, WIV-ISP, Brussels, Belgium
- L. Gamet-Payrastre, UMR 1089 Xénobiotiques, INRA, Toulouse, France
- P. Groenewegen, Professor of Sociology, NIVEL, The Netherlands
- T.H.J.J. van der Hagen, Professor of Reactor Physics, Faculty of Applied Sciences, Technical University, Delft, The Netherlands
- J.J. Heimans, Professor of Neurology, VU Medical Center, Amsterdam, The Netherlands
- L. Hens, Professor of Human Ecology, College HGR, Belgium
- M. Hunink, Professor of Clinical Epidemiology and Radiology, University Medical Center, Rotterdam, The Netherlands
- C. Infante-Rivard, Professor of Epidemiology, Faculty of Medicine, McGill University, Montréal, Canada
- J.C. de Jongste, Professor of Paediatric Respiratory medicine, University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
- G. Kok, Professor of Applied Psychology, Maastricht University, Maastricht, The Netherlands

- A. Knottnerus, Professor of General Practice, Scientific Council for Government Policy, The Hague, The Netherlands
- J. Leer, Professor of Radiotherapy, University Nijmegen Medical Center, Nijmegen, The Netherlands
- J. Mackenbach, Professor of Public Health, University Medical Center, Rotterdam, The Netherlands
- R. Marcos-Gragera, Unitat d'Epidemiologia i Registre de Càncer de Girona, Institut d'Investigació Biomèdica de Girona, Spain
- P. Martens, Professor of Sustainable Development, International Center for Integrated Assessment & Sustainable Development (ICIS), Maastricht University, Maastricht, The Netherlands
- J. van der Meer, Professor of Medicine, Nijmegen Institute for Infection, Inflammation and Immunity, University Nijmegen Medical Center, Nijmegen, The Netherlands
- G. Mulder, Emeritus Professor of Toxicology, Oegstgeest, The Netherlands
- J.G. Nijhuis, Professor of Gynaecology-perinatology, Maastricht University Medical Center, Maastricht, The Netherlands
- D. van Norren, Emeritus Professor of Ophthalmic Physics, Leusden, The Netherlands
- M. de Ridder, Occupational and Environmental Health, Public health department, Ghent University, Belgium
- S. de Sanjosé, Unit of Infections and Cancer, Cancer Epidemiology Research Programme, Institut Català d'Oncologia, Spain
- M.C. Turner, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada
- J. Vanderstraeten, Research Center on Environmental Health and Work Health, School of Public Health, Université Libre de Bruxelles, Belgium
- A.L.M. Verbeek, Professor of Clinical Epidemiology, Department of Epidemiology, Biostatistics and HTA, University Nijmegen Medical Center, Nijmegen, The Netherlands
- S.P. Verloove-Vanhorick, Emeritus Professor of Paediatrics, Oegstgeest, The Netherlands
- M. Verweij, Public Health Ethics, Ethics Institute, Department of Philosophy, Utrecht University, Utrecht, The Netherlands
- C. Vleminckx, Unit Toxicology, Public Health and Surveillance, Brussels, Belgium
- D.T. Wigle, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

C ALL/AML: CCG Evidence Summary

This annex contains summary tables of the evidence summary of the systematic review of reviews, performed by the Cochrane Childhood Cancer Group (CCG), in which ALL and AML were considered separately. [225]

C.1 Physical risk factors

Ionising radiation

Table C1. Short summary of the selected systematic review on pre- and postnatal diagnostic X-rays [a].[226]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Pre- / postnatal diagnostic X-rays	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [b]	Quality of systematic review/meta-analysis [c]
Prenatal	ALL	1 individual	0.95 (0.73-1.23)	6/9 (67%)
	AML	1 individual	2.35 (0.79-7.00)	
Postnatal	ALL	1 individual	**1.63 (1.43-1.85)**	

[a] The specific purpose of this review was to study the hypothesis that the association between prenatal and postnatal radiation exposure and childhood leukaemia would have become less strong, given technological improvements and the shift to non-ionising imaging technologies (ultrasound). The authors concluded that their results might be interpreted as a confirmation of this hypothesis, underlining, however, that the results do not contradict previous evidence accumulated since 1956, indicating risk increases associated with prenatal X-ray exposure.

[b] OR: odds ratio, CI: confidence interval.

[c] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Table C2. Short summary of selected systematic review on residential proximity to nuclear facilities.[227]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Endpoint	Type of leukaemia	Number of pooled or individual studies	Results	Quality of systematic review/meta-analysis [a]
Living closer to nuclear facility	ALL	1 individual	Higher risk [b] (significance level not stated)	1/9 (11%)

[a] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

[b] The conclusions in the 'CCG Evidence Summary are based on one Swedish study, selected from the French review, as this was the only study that explicitly mentioned the type of leukaemia (ALL).[228] There is a problem with this study as the conclusion of the reviewers in the original French research report ('Risque de leucémies pas plus élevé à proximité des sites qu'ailleurs')[129] differs from that published in an international journal in a special issue with the proceedings of a childhood leukaemia workshop ('Risk of leukaemia higher close to NPP than elsewhere'). It appears that the conclusion in the French research report is the correct one.

Extremely low-frequency (ELF) magnetic fields

Table C3. Short summary of selected systematic reviews on ELF magnetic fields.[18,140]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Extremely low-frequency (ELF) magnetic fields	Type of leukaemia	Number of pooled or individual studies	Results OR/RR (95% CI) [a]	Quality of systematic review/ meta-analysis [b]
Residential magnetic fields:[140] different definitions and subgroups [c]	ALL	> 2 individual	(Non-) significant higher risks	1/10 (10%)
≥ 0.4 μT	ALL	Pooled (unclear nr)	**2.1 (1.3–3.3)**	
Electric blankets: prenatal use	ALL	1 individual	**1.6 (1.1-2.3)**	
postnatal use	ALL		**2.8 (1.5-5.0)**	
Exposed to magnetic fields ≥0.4 μT (as compared to <0.1 μT)[18]	ALL	1 individual	**4.73 (1.14-19.7)**	1/9 (11%)
	AML	1 individual	Risk not increased (no further information available)	

[a] OR: odds ratio, RR: risk ratio, CI: confidence interval.

[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

[c] 24-hour or spot measurements in one or more rooms, wire-codes, distance and relative load for power lines, exposure from different electrical appliances, etc.

C.2 Chemical risk factors

Parental occupational exposure to pesticides

Table C4. Short summary of selected systematic review on parental occupational pesticide exposure.[166]
(A detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Parental occupational pesticide exposure	Type of leukaemia	Number of combined or individual studies	Results OR (95% CI) [a]	Quality of systematic review/ meta-analysis [b]
Paternal (preconceptual)	ALL	8	1.30 (0.86-1.95)	5/10 (50%)
	AML	4	1.13 (0.59-2.14)	
Maternal (prenatal)	ALL	6	**2.64 (1.40-5.0)**	
	AML	4	**2.64 (1.47-4.74)**	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Residential exposure to pesticides

Table C5. Short summary of selected systematic review on residential pesticide exposure.[167]
(A detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Residential pesticide exposure	Type of leukaemia	Number of combined or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
During pregnancy	ALL	5	**2.04 (1.54-2.68)**	6/10 (60%)
	AML	3	1.44 (0.81-2.59)	
During childhood	ALL	4	1.40 (0.90-2.16)	
	AML	2	1.71 (0.77-3.80)	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Arsenic exposure in drinking water

Table C6. Short summary of selected systematic review on arsenic exposure in drinking water.[195]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Arsenic exposure in drinking water	Type of leukaemia	Number of combined or individual studies	Results	Quality of systematic review/meta-analysis [a]
Prenatal	ALL	1 individual	Non-significantly lower risk	0/9 (0%)
Postnatal	ALL	1 individual	Non-significantly higher risk	

[a] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Parental tobacco smoking

Table C7. Short summary of selected systematic review on parental tobacco smoking.[198]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews[225])

Exposure to passive smoking from parents	Type of leukaemia	Number of pooled or individual studies	Results OR/RR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
From mother during pregnancy; several subgroups[c]	ALL	6 individual	Inconsistent results	2/11 (18%)
	AML	2 individual	Inconsistent results	
From mother before pregnancy	ALL	1 individual	2.1 (1.0-4.3)	
From father; several subgroups	ALL	4 pooled	1.17 (0.96-1.42)	
	AML	3 individual	Inconsistent results	

[a] OR: odds ratio, RR: risk ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.
[c] Number of cigarettes per day or any smoking.

Parental marijuana smoking

Table C8. Short summary of selected systematic review on parental marijuana smoking.[201]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Marijuana (cannabis) smoking by parents	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Maternal use during or in the year before pregnancy	AML	1 individual	**11.0 (1.42-85.20)**	1/9 (11%)
Paternal use	AML	1 individual	1.47 (CI: not provided; p=0.32)	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Parental alcohol consumption

Table C9. Short summary of selected systematic review on parental alcohol consumption.[202]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Parental alcohol consumption	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Maternal alcohol consumption				
Year before pregnancy	ALL	1 individual	1.2 (0.9-1.5)	1/10 (10%)
Month prior to pregnancy	ALL	2 individual	Inconsistent results	
	AML	1 individual	**1.8 (1-3.3)**	
During pregnancy; several subgroups [c]	ALL	> 2 individual	Inconsistent results	
	AML	> 2 individual	Inconsistent results	

During breast-feeding	ALL	2 individual	Inconsistent results
	AML	1 individual	0.8 (0.3-1.9)
Paternal alcohol consumption			
Month prior to conception; several subgroups	ALL	> 2 individual	Inconsistent results
	AML	> 2 individual	Inconsistent results
Exposure period not stated	ALL	1 individual	1.2 (0.8-1.9)
One year prior to conception	AML	1 individual	1.5 (0.6-3.5)

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.
[c] Prior to conception, first, second or third trimester, number of glasses, type of drinks.

C.3 Infectious agents and other factors

Different infectious exposures

Table C10. Short summary of selected systematic review on different infectious exposures.[212]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Different infectious exposures	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Different maternal infections	ALL	> 2 individual	(Non-) significantly higher risk	0/9 (0%)
Different childhood infections	ALL	> 2 individual	Inconsistent results	
Different vaccinations	ALL	> 2 individual	Inconsistent results	
Birth order; several subgroups	ALL	> 2 individual	Inconsistent results	
	AML	1 individual	**1.59 (1-2.53)**	
Paternal occupational social contact levels	ALL	1 individual	**1.5 (1.1-2.1)**	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Early social contacts

Table C11. Short summary of selected systematic review on early social contacts.[215]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Day-care attendance and other early social contacts	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Day-care attendance or social contacts; different definitions and subgroups [c]	ALL	> 2 individual	(Non-) significantly lower risks	4/11 (36%)
	common-ALL [d]	7 pooled	**0.83 (0.70-0.98)**	
		> 2 individual	(Non-) significantly lower risks	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.
[c] Day-care attendance, preschool playgroup, regular contact with children from outside home or social activities at different age or in different intensity.
[d] Most frequent type of ALL: common B-cell precursor ALL (cALL).

Allergies

Table C12. Short summary of selected systematic review on allergies.[216]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Different types of allergy	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Overall allergy	ALL	8 pooled	0.67 (0.54-0.82)	5/11 (45%)
	AML	3 individual	Non-significantly lower risk	
Asthma	ALL	6 pooled	0.82 (0.63-1.10)	
Hay fever	ALL	5 pooled	**0.53 (0.43-0.65)**	
Eczema	ALL	5 pooled	**0.68 (0.56-0.83)**	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Breast-feeding

Table C13. Short summary of selected systematic review on breast-feeding.[217]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Breast-feeding	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Breast-feeding	ALL	17 pooled	**0.91 (0.84-0.98)**	6/11 (55%)
	AML	9 pooled	0.88 (0.76-1.02)	
Duration of breast-feeding < 6 months	ALL	12 pooled	0.93 (0.86-1.00)	
	AML	8 pooled	0.97 (0.81-1.17)	
Duration of breast-feeding > 6 months	ALL	13 pooled	**0.81 (0.72-0.91)**	
	AML	9 pooled	**0.72 (0.57-0.91)**	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Maternal folate and vitamin supplementation

Table C14. Short summary of selected systematic review on maternal folate and vitamin supplementation.[221]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Maternal folate and vitamin supplementation	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Vitamins with folate versus no folate during pregnancy	ALL	2 pooled	1.06 (0.77-1.46)	1/11 (9%)
Vitamins with folate versus no vitamins during pregnancy	ALL	2 pooled	1.02 (0.86-1.21)	
Vitamins before pregnancy	ALL	2 pooled	0.95 (0.95-1.18)	
Vitamins only before pregnancy	ALL	2 pooled	1.05 (0.55-2.01)	
Vitamins during pregnancy	ALL	5 pooled	**0.83 (0.73-0.94)**	
Folate before pregnancy	ALL	1 individual	1.63 (0.55-4.82)	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Birth weight

Table C15. Short summary of selected systematic review on birth weight.[222]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Birth weight	Type of leukaemia	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
High birth weight compared to normal birth weight	ALL	23 pooled	**1.24 (1.18-1.33)**	2/11 (18%)
	AML	9 pooled	**1.24 (1.16-1.32)**	
Low birth weight	ALL	10 pooled	0.97 (0.81-1.16)	
	AML	9 pooled	**1.50 (1.05-2.13)**	
Per kilogram increase in birth weight	ALL	16 pooled	**1.18 (1.12-1.23)**	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Socio-economic status

Table C16. Short summary of selected systematic review on socio-economic status.[223]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[225])

Socioeconomic status	Type of leukaemia	Number of pooled or individual studies	Results	Quality of systematic review/meta-analysis [a]
Family income	ALL	4 individual	Inconsistent results	2/9 (22%)
	AML	1 individual	Higher AML rates significantly associated with a lower socioeconomic status	
Mother's education	ALL	6 individual	Inconsistent results	
	AML	1 individual	Higher AML rates non-significantly associated with a lower socioeconomic status	
Father's education	ALL	4 individual	Higher ALL rates (non-) significantly associated with a higher socioeconomic status	
	AML	2 individual	Higher AML rates (non-) significantly associated with a lower socioeconomic status	
Father's occupational class	ALL	2 individual	Higher ALL rates non-significantly associated with a higher socioeconomic status	
Household density	ALL	1 individual	Higher ALL rates non-significantly associated with a higher socioeconomic status	
Derived measure (i.e. combining father's education and occupation)	ALL	1 individual	Higher ALL rates non-significantly associated with a lower socioeconomic status	
Ecological measures (i.e. both education and occupational class)	ALL	1 individual	**Higher ALL rates significantly associated with a higher socioeconomic status**	

[a] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

D Childhood leukaemia in general: Evidence Summary

This annex contains summary tables of the evidence summary of the systematic review of reviews in which childhood leukaemia in general was considered.[213]

D.1 Physical risk factors

Ionising radiation

Table D1. Short summary of the selected systematic review on pre- and postnatal diagnostic X-rays [a]. [226]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Pre- / postnatal diagnostic X-rays	Number of pooled or individual studies	Results OR / SIR / SMR (95% CI) [b]	Quality of systematic review/meta-analysis [c]
Prenatal	9 pooled	0.99 (0.87-1.13)	8/10 (80%)
Postnatal	1 individual	**1.29 (1.04-1.60)**	
	3 individual	Non-significant results	

[a] The purpose of this review was to study the hypothesis that the association between prenatal and postnatal radiation exposure and childhood leukaemia would have become less strong, given technological improvements and the shift to non-ionising imaging technologies (ultrasound). The authors concluded that their results might be interpreted as a confirmation of this hypothesis, underlining, however, that the results do not contradict previous evidence accumulated since 1956, indicating risk increases associated with prenatal X-ray exposure.

[b] OR: odds ratio, SIR: standardized incidence ratio, SMR: standardized mortality ratio, CI: confidence interval.

[c] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Table D2. Short summary of selected systematic review on residential proximity to nuclear facilities.[227]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Endpoint	Number of pooled or individual studies	Results	Quality of systematic review/meta-analysis [a]
Living closer to nuclear facility	25 individual	No significance levels given	2/10 (20%)

[a] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Extremely low-frequency (ELF) magnetic fields

Table D3. Short summary of selected systematic reviews on ELF magnetic fields.[18,140]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Extremely low-frequency (ELF) magnetic fields	Number of pooled or individual studies	Results OR/RR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Residential magnetic fields:[140] different types of studies, different definitions and subgroups [c]	22 individual	**(Non-)significant higher risks**	2/10 (20%)
≥0.4 μT	9 pooled	**2.0 (1.3-3.1)**	
Electric blankets, pre- and postnatal use	3 individual	Inconsistent results	
Hair dryer	1 individual	**2.8 (1.4-6.3)**	
Distance to transmission lines <49 m (as compared to > 600 m) [18]	1 individual	1.67	1/10 (10%)
Exposure to magnetic fields ≥0.4 μT (as compared to <0.1 μT)	1 individual	2.63 (0.77-8.96)	

[a] OR: odds ratio, RR: risk ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.
[c] Prior to conception, first, second or third trimester, number of glasses, type of drinks.

Diagnostic ultrasound scans

Table D4. Short summary of selected systematic reviews on diagnostic ultrasound scans.[156]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Diagnostic ultrasound scans[156]	Number of pooled or individual studies	Results	Quality of systematic review/ meta-analysis [a]
Ultrasound exposure in utero	3 individual	Neither higher or lower risk	3/10 (30%)

[a] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

D.2 Chemical risk factors

Parental occupational exposure to pesticides

Table D5. Short summary of selected systematic review on parental occupational pesticide exposure.[166]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Parental occupational pesticide exposure	Number of combined or individual studies	Results OR (95% CI) [a]	Quality of systematic review/ meta-analysis [b]
Paternal (preconceptional)			7/11 (64%)
- any pesticides	30 pooled	1.09 (0.88-1.34)	
- insecticides	3 pooled	**1.43 (1.06-1.92)**	
- herbicides	5 pooled	1.25 (0.94-1.66)	

- fungicides	4 pooled	1.66 (0.87-3.17)
Maternal (prenatal)		
- any pesticides	16 pooled	**2.09 (1.51-2.88)**
- insecticides	6 pooled	**2.72 (1.47-5.04)**
- herbicides	2 pooled	**3.62 (1.28-10.3)**

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Residential exposure to pesticides

Table D6. Short summary of selected systematic review on residential pesticide exposure.[167]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Residential pesticide exposure	Number of combined or individual studies	Results OR (95% CI) [a]	Quality of systematic review/ meta-analysis [b]
During pregnancy			8/11 (73%)
- unspecified	11 pooled	**1.54 (1.13-2.11)**	
- insecticides	8 pooled	**2.05 (1.80-2.32)**	
- herbicides	5 pooled	**1.61 (1.20-2.16)**	
During childhood			
- unspecified	9 pooled	**1.38 (1.12-1.70)**	
- insecticides	7 pooled	**1.61 (1.33-1.95)**	
- herbicides	4 pooled	0.96 (0.59-1.58)	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Maternal cured meat intake

Table D7. Short summary of selected systematic review on maternal cured meat intake.[205]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Maternal cured meat intake	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/ meta-analysis [b]
Intake level	3 individual	Non-significantly higher risk	4/10 (40%)
Meat type:	1 individual	(no significance level given)	
hotdogs		0.9	
bacon & sausages		1.5	
lunch meat		1.0	
Ham		1.5	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

D.3 Infectious agents and other factors

Different infectious exposures

Table D8. Short summary of selected systematic review on different infectious exposures.[212]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Different infectious exposures	Number of pooled or individual studies	Results OR (95% CI) [a]	Quality of systematic review/meta-analysis [b]
Different maternal infections	> 2 individual	(Non-) significantly higher risks	
Different childhood infections	> 2 individual	Inconsistent (non) significant results	
Different vaccinations	> 2 individual	Non-significant results, except for **significant lower risk for 'immunisations'**	
Birth order; several subgroups	> 2 individual	Conflicting results	
Paternal occupational social contact levels	> 2 individual	Inconsistent results	

[a] OR: odds ratio, CI: confidence interval.
[b] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

Socio-economic status

Table D9. Short summary of selected systematic review on socio-economic status.[223]
(A more detailed summary is presented in the original CCG Evidence summary of systematic reviews.[213])

Socioeconomic status	Number of pooled or individual studies	Results	Quality of systematic review/meta-analysis [a]
Family income	1 individual	Non-significant higher risk	3/10 (30%)
	4 individual	**Significant lower risks**	
	3 individual	Non-significant lower risks	
Mother's education	2 individual	**Significant higher risks**	
	4 individual	Non-significant higher risks	
	5 individual	**Significant lower risks**	
	2 individual	Non-significant lower risks	
Father's education	2 individual	Non-significant higher risks	
	4 individual	**Significant lower risks**	
	3 individual	Non-significant lower risks	
Father's occupational class	3 individual	**Significant higher risks**	
	5 individual	Non-significant higher risks	
	1 individual	**Significant lower risk**	
	2 individual	Non-significant lower risks	
Household density	1 individual	**Significant higher risk**	
	1 individual	Non-significant higher risk	
	1 individual	Non-significant lower risk	
Derived measure (i.e. combining father's education and occupation)	1 individual	Non-significant lower risk	
Highest parental education	3 individual	Inconsistent results	

[a] Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria.

E Causality considerations and limitations

The Committee has focussed in this report on epidemiological studies. In such observational studies the quality of exposure assessment is crucial, especially in deriving dose response relations.[229] Moreover, the reduction of bias and the adjustment for confounding factors are important in assessing the evidence for causality of associations. The data presented in chapters 4-6 show that some associations have been found, but these cannot be taken as proof of causality. One standard tool in assessing evidence for causality are Bradford Hill's considerations: strength, consistency, specificity, temporality, biological gradient (or exposure-response), plausibility, coherence, experiment, analogy.[14,15]

E.1 The Bradford Hill considerations

Bradford Hill emphasised that none of the following nine considerations can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. So, absence does not disprove causality, only presence is considered a contributing argument that causality exists.

Strength

A relative risk or odds ratio higher than 2 would usually be considered a relatively strong association. However, few environmental risk factors of disease reach such values. Also as there is often substantial misclassification of exposure, this mostly leads to underestimation of the real risk, thus decreasing the strength. In this report most of the relative risks and odds ratios are too low (< 2-3) to be considered as contributing to the strength argument.

Consistency

Consistency of results from different studies strengthens the causality argument. However, different exposure situations are often not identical, which makes it very hard for environmental causes to fulfil this criterion. In this report most of the evidence for individual exposures comes from a limited number of studies. As in the previous consideration, the absence of consistency does not disprove causality, the argument is just not strengthened.

Specificity

Specificity of outcome means that the exposure is not associated with different adverse outcomes. The literature evaluated in this report is often focussed on childhood leukaemia and other diseases/outcomes are usually not considered. This does not mean that other outcomes do not occur, the information on that is simply not available. However, in general specificity is one of the weakest considerations, as it very rarely the case that only one carcinogen causes disease.

Temporality

Risk factors for childhood leukaemia can mostly only be investigated in case-control studies. This means that exposure is measured retrospectively, so temporality can never truly be addressed like in prospective cohort studies. This is a considerable problem, as temporality is a crucial consideration. A potential cause cannot be an actual cause if the exposure occurred after the disease developed. It should be noted that various biases in case-control studies, such as responder and recall bias, might influence the recall of timing of exposure. Ultimately only prospective cohort studies can solve this, but these are rare in the collection of investigations reviewed in this report.

Biological gradient or exposure-response

Exposure-response relationships can only be assessed if exposure can be measured adequately and with sufficient precision.[229] However, since often only the use of questionnaires or at best spot-sampling are available methods, exposure assessment is difficult and often also done poorly.

A complicating factor with childhood leukaemia is that exposure can occur at different phases in the development of a child: before, during and after pregnancy. Exposure of the parent to environmental factors before conception or during the pregnancy may both related to genetic or epigenetic damage, the latter for instance by enhanced proliferation of cells.[230] Effects of exposure at an early stage of pregnancy may differ from exposure at a later stage and from postnatal exposure.

Another problem is that in practice children and their parents are exposed to mixtures of different agents, but there is hardly any study performed on interactions, not only of agents, but also between prenatal and postnatal exposures.

Plausibility

This refers to the understanding of the biological model behind the causality of the exposures in questions. If there is information available, the argument for

causality is strengthened, but for many suspected carcinogens the quantitative details of biological model are unknown.

Coherence

This argument means that the cause and effect interpretation should not seriously conflict with the generally known facts of the natural history and biology of the disease. However, as in reality little is known about the natural history of childhood leukaemias besides their clinical features, it is not a useful consideration in the framework of this report.

Experiment

Data from experimental studies, showing evidence for effects, may strengthen the biological plausibility of an association. Of course for childhood leukaemia only animal experiments are acceptable. However, the question is whether the animals used (mostly rodents) are an adequate model for humans and how the doses given to the animals are comparable to doses in humans. For exposure around pregnancy the timing of the exposure may well be different also.

Analogy

According to Bradford Hill, it would in some circumstances be fair to judge by analogy. This means that if it is known that the effect of one type of exposure can lead to childhood leukaemia, a similar effect from another type of exposure might also. However, the variety of types of exposure addressed in this report is so wide and so little is known about these exposures, that analogy is not a very useful consideration in practice.

E.2 Chance, bias and confounding

In addition to the Bradford Hill considerations and the strength of evidence, alternative explanations for epidemiological associations other than causality should be considered: chance, bias (specifically exposure misclassification) and confounding. If these are unlikely, a causal relation is more likely. In particular in situations of sparse epidemiological evidence and a lack of information on these factors, judgements about the causal nature of reported associations between exposures and childhood leukaemia have to be made with caution.

Chance

If associations are observed in epidemiological studies, it needs to be determined whether they can be explained by either chance or a particular cause. By definition there is a five-percent likelihood that a 'statistically significant' association will be found that can be attributed to chance (a 'false positive'). If several statistical tests (multiple comparisons) are made, a 'statistically significant' association will be attributable to coincidence in one in twenty tests. On the other hand, not finding an association can also be a chance finding (a 'false negative').

Bias

Effect measured in epidemiological studies can be biased in three ways: through selection bias, information bias or confounding.[10] They differ for different types of studies, such as cohort and case-control studies.

Selection bias. Selection bias may occur as a result of the way the study population is selected. In case-control studies, participants enter the study based on being ill (cases) or explicitly not having the disease of interest (controls). The selection that occurs at the start of the study can already bias the results. In some studies the selection of both cases and controls is conducted within one or several hospitals. However, the patterns of hospital admission can be different for different diseases. For instance, if the hospital is the only possible treatment facility for cancer in the region but there are many smaller hospitals for e.g. emergencies, the hospital treating cancer will cater for different populations for the cancer patients than for its emergency ward patients. If the controls are recruited from the latter groups, the cases and controls are drawn from different populations that might not be comparable. Population-based case-control studies suffer less from this selection bias, but in these studies it needs to be clear that the controls are truly representative for the same community as the cases.[231] Response rates in case-control studies need to be high enough for the study population to be representative of the population it stems from, ideally at least 70%, and they also need to be sufficiently similar between cases and controls.

Information bias. Information bias can occur through misclassification of health effects as well as through misclassification of the exposure.

Misclassification of effect. Misclassification of effects may, for example, occur as the result of differences in reporting, diagnostics, registration, coding, admission and treatment policy, or availability and accessibility of health care.

Misclassification of exposure. Quantification of exposure is almost always very crude and this lack of precision leads to a flattening of the exposure-response curve.[232] Misclassification can also occur if the exposure occurred many years before the health effects, making it difficult to measure the exposure in question. If the misclassification of the exposure occurs proportionally in the case and control population, the result generally underestimating the risk.[233]

Reduction of information bias: blinding. In case-control studies it is impossible to blind the cases for the diagnosis. Once diagnosed, patients will search for explanations of their illness. They are likely to report their past exposure for any potential cause differently from controls who do not have this incentive. As patients are often clearly ill, it is also virtually impossible to blind interviewers for the disease status, thus allowing for suggestive interviewing in either direction. Blinding the observers through the use of mailed-in or web-based questionnaires is the only way to control this. Even telephone interviews are often not blinded, as patients are likely to reveal their disease status.[231]

Confounding

Health status depends on many factors, including age, sex, level of urbanisation, socio-economic status, ethnicity, smoking habits and other lifestyle factors. Availability of health services can also affect the health status. The effect of these factors may differ considerably from one situation to another, which increases the risk of confounding the study on the relationship between environmental exposure and disease, especially if associations are weak.

A confounding factor is described as a known risk factor that is associated with the exposure being studied, but that is not an intermediary factor in the causal relationship between exposure and effect.[10] If there are sufficient data on relevant risk factors, it is possible to adjust for confounding. They need to be controlled for and thus measured. Age, sex, social-economic status and education are common confounders, but other factors are also possible. Matching of cases and controls can be a way to control confounding, but in some cases can introduce confounding also, so over-matching should be avoided.[231]

F Classifications of evidence

IARC-classification of scientific evidence

To characterise the strength of evidence for a causal relation between exposure to environmental factors and cancer IARC[16] developed a classification based on:

- Epidemiological evidence
- Animal experimental evidence and
- Mechanistic and other evidence.

The evidence from studies in humans and experimental animals is classified into one of the following categories:

- *Sufficient* evidence of carcinogenity
- *Limited* evidence of carcinogenity
- *Inadequate* evidence of carcinogenity
- Evidence suggesting *lack* of carcinogenity.

Together with the available mechanistic and other evidence the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenity of the agent to humans. The following categories are distuinguished:

- Group 1: the agent is *carcinogenic t*o humans
- Group 2A: the agent is *probably carcinogenic* to humans
- Group 2B: the agent is *possibly carcinogenic* to humans
- Group 3: the agent is *not classifiable* as to its carcinogenicity to humans
- Group 4: the agent is *probably not carcinogenic* to humans.

This classification cannot as such be used in the present report, since experimental and mechanistic evidence is not considered in detail.

Wigle-classification of epidemiological evidence

Wigle expressed the IARC-classification of epidemiological evidence for causal relationships between child health outcomes and environmental chemical contaminants as three ‘levels of evidence’: sufficient, limited or inadequate, according to predefined criteria of the U.S. National Academy of Sciences (Table F1).[17]

Table F1. Wigle's classification of epidemiological evidence.

Level of evidence	Definition
Sufficient	At least one expert group has reviewed the available evidence and published a peer-reviewed report indicating a consensus view that there is a causal relationship.
Limited	Limited evidence is suggestive of an association between the agent and the outcome but is limited (and may or may not represent a causal relationship) because chance, bias and confounding cannot be ruled out with confidence, *e.g.* at least one high quality study shows a positive association but the results of other studies are inconsistent.
Inadequate	Available studies are of insufficient quality (*e.g.* available studies have failed to adequately control for confounding or have inadequate exposure assessment), consistency or statistical power to permit a conclusion regarding the presence or absence of an association or no studies exist that examine the relationship.

About the Superior Health Council of Belgium and the Health Council of the Netherlands

The Superior Health Council

The Superior Health Council (SHC) is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send a mail to info.hgr-css@health.belgium.be.

The Health Council of the Netherlands

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

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