Residential exposure to solar ultraviolet radiation and incidence of childhood hematological malignancies in France

Astrid Coste[1], Stéphanie Goujon[1,2], Mathieu Boniol[3], Fabienne Marquant[1], Laure Faure[1,2], Jean-François Doré[4], Denis Hémon[1], Jacqueline Clavel[1,2]

[1] Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), INSERM, UMR 1153, Epidemiology of childhood and adolescent cancers research group (EPICEA), Paris Descartes University, F-75014 Paris, France
[2] French National Registry of Childhood Hematological Malignancies (NRCH), Villejuif, France
[3] University of Strathclyde Institute of Global Public Health at iPRI, International Prevention Research Institute, Lyon, France
[4] Cancer Research Center of Lyon (CRCL), INSERM UMR 1052 CNRS 52B6, Centre Léon Bérard, 28 rue Laënnec, F-69373 Lyon Cedex 08, France

Abbreviations:

UV: ultraviolet; CHM: childhood hematological malignancies; AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; PBC-ALL: precursor B-cell acute lymphoblastic leukemia; NHL: Non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma

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Correspondence:

Astrid Coste, PhD student, Epidemiology of childhood and adolescent cancers research group (EPICEA), Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), INSERM, UMR 1153, Paris Descartes University, F-75014 Paris, France, Tel:+33145595292, Fax: +33145595151, E-mail:astrid.coste@inserm.fr

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Purpose Few studies have investigated the relationship between solar ultraviolet radiation (UV) and childhood hematological malignancies (CHM). This study addresses the associations between residential UV exposure at diagnosis and the incidence of types and subtypes of CHM, by age and gender, in France, over a long period, on the fine scale of the 36,326 *Communes* that constitute mainland France. **Methods** The 9,082 cases of acute leukemia (AL) and 3,563 cases of lymphoma diagnosed before the age of 15 years from 1990 to 2009 were provided by the French National Registry of Childhood Hematological Malignancies. The incidence of CHM was calculated by *Commune,* year, age and gender and expressed as the standardized incidence ratio (SIR). UV data from 1988 to 2007 were extracted from the EUROSUN database. **Results** The annual daily average UV exposure of the children ranged from 85.5 to 137.8 J/cm^2. For each additional 25 J/cm^2 there was a significant increase in precursor B-cell acute lymphoblastic leukemia (PBC-ALL) in children aged less than 5 years (SIR: 1.18; 95%CI: 1.10-1.27). Further analysis of PBC-ALL in the young children suggested a better fit of models with a threshold, with the risk increasing above 100 J/cm^2, for which the SIR was 1.24 (95%CI: 1.14-1.36) for a 25 J/cm² increase. The results remained stable in analyses stratifying by deprivation index or degree of urbanization of the *Communes*. **Conclusion** The study suggests that higher residential UV exposure may be positively associated with a higher incidence of PBC-ALL in early childhood.

I. **Introduction**

Acute leukemia (AL) and lymphoma are the most frequent childhood hematological malignancies (CHM). Several genetic diseases and polymorphisms[1], and non-genetic exposures (including ionizing radiation and, for Hodgkin's and Burkitt's lymphoma, Epstein Barr virus) are known risk factors. Some factors related to early immune stimulations and environmental exposures (pesticide use at home and, for AL, extremely low frequency electromagnetic fields) are also suspected[2, 3].

Solar ultraviolet (UV) radiation, UVA (315 - 400 nm) and UVB (280 - 315 nm), exposures are ubiquitous with marked gradients within and between countries.

Solar UV radiation, a known risk factor for skin cancers[4], plays a role in vitamin D synthesis and, through this mechanism, has also been identified as a potential protective factor for some cancers[5, 6]. UV radiation, especially UVB radiation, may also induce systemic immune suppression. Animal study findings have raised the question of whether UV radiation may influence the development of hematological malignancies by means of its immunosuppressive effect[7–9].

The effects of UV radiation on human health are multiple and complex, and may act in positive or negative ways on the emergence of hematological malignancies. The general population's exposure to solar UV radiation is known to have increased in recent decades. In addition to experimental biological investigations of the association between UV radiation and the incidence of hematological malignancies, the results of which are still not conclusive, epidemiological studies have been conducted. The results are mixed for adults and only four studies have been published for children.

The association between the incidence of non-Hodgkin's lymphoma (NHL) and UV radiation exposure among adults has been much studied in the last 20 years. However, the results remain a subject of debate. Most North-American studies and a few others, including pooled studies, have found an inverse association between UV radiation exposure and NHL incidence[10–13]. However, some studies found a positive association[14–16]. There have been few studies of leukemia and Hodgkin's lymphoma, and UV radiation exposure. Most of the studies conducted have found an inverse association between UV radiation and cancer incidence [17–20]. An ecological study in Japan found a positive correlation between UVB radiation level and leukemia mortality risk, but only for two

subtypes: 'lymphoid leukemia' and 'other malignant neoplasms of lymphoid and histiocytic tissue'[21].

To the authors' knowledge, four studies, with different designs and sample sizes, on the association between childhood hematological malignancies and UV radiation exposure have been published. Three studies found a negative association, for leukemia [22,24] and/or NHL [23,24], while the fourth study [25] showed an increased risk of lymphoblastic leukemia in 2-4-year-old children during the light season (April-September).

In that context, the objective of the present study was to analyze the association between population exposure to UV radiation and the incidence of types and subtypes of CHM, over a long time period.

II.   Materials and Methods

The association between the UV exposure of the subjects' places of residence at the time of diagnosis and the incidence rates of CHM was studied. For this purpose, quantitative estimates of average annual exposures to UV radiation for the 1988-2007 period of the 36,326 French Communes, the smallest administrative subdivisions of the country, were associated with the incidence data of the corresponding Communes of France by year, age and gender.

Cases, time period, geographic units and population counts

The CHM cases were provided by the French National Registry of Childhood Hematological Malignancies (NRCH)[26]. Since 1990, the registry has included all the malignant or borderline hematological diseases occurring in children aged less than 15 years residing in mainland France at the time of diagnosis. For each case, the registry provided the date of birth, date of diagnosis and address where the child was living at the time of diagnosis. All the CHM cases diagnosed between 1990 and 2009 and having a known residential *Commune* at diagnosis were included (99.9% of the cases). For the study period (1990-2009), 9,082 cases of AL and 3,563 cases of lymphoma were included.

An incidence study was performed at the *Commune* level over the study period. The cases consisted in all children diagnosed with AL or lymphoma before the age of 15 years and registered in the NRCH during the period. The annual national CHM incidence rates estimated by the NRCH, by age and gender, were used as reference rates. The annual estimates of the *Commune* populations, by year of age and gender, were provided by the French National Institute for Statistics and Economic Research (INSEE) for the census years: 1990, 1999, 2006, 2007, 2008 and 2009. For the other years, the estimates for the *Communes* were interpolated using the annual estimates provided by INSEE for the 96 French mainland *Départements* (larger administrative units with an average of 360 *Communes* per *Département*).

UV radiation exposure at the time of diagnosis

UV radiation exposure data were provided by the European EUROSUN project, the aims of which are to quantify sun exposure in Europe and its effects on health. The European Meteosat satellites provided images from which an assessment of solar surface irradiance (SSI) was obtained for the 1988-2007 period (HelioClim-1 database for 1988-2005, HelioClim-3 database for 2004-2007). SSI is the solar irradiance observed at ground level on horizontal surfaces and is integrated over the whole spectrum[27]. An algorithm enables derivation of the spectral distribution every 10 nm from the total irradiance observations. The EUROSUN data provide an assessment of UVA and UVB radiation in Europe on a 5 x 5 km grid. Each *Commune* was allocated the annual average UVA and UVB radiation estimated at the location of the town hall. The spatial correlation between UVB and UVA radiation exposures was almost equal to 1. Consequently, the associations of UVA and UVB radiation exposures with CHM could not be analyzed separately and the exposure variable used for a given

Commune was therefore the daily average UV (UVA+UVB) radiation exposure over the period 1988-2007.

Statistical analysis

All analyses were implemented with SAS v9.3 software.

The standardized incidence ratio (SIR) was used to characterize the spatial differentials of incidence over the study period. The SIR was calculated as the ratio of the observed number of cases to the corresponding expected number of cases obtained from the *Commune* numbers of at-risk person-years (PY), by age (1 year) and gender, and the national annual age- and gender-specific incidence rates.

Poisson regressions were fitted for all the analyses using the *Communes* of residence at diagnosis as the basic statistical unit, with their expected number of cases (E_i) as the offsets and observed number of cases (O_i) as the observations. As most of the analyses which were performed on this small scale led to under-dispersion, *Communes* were grouped using the decile of the covariate of interest.

Since there were no prior hypotheses with regard to the shape of the relationship between leukemia or lymphoma incidence and sun exposure, two models were compared using the log-likelihood test to determine the degree of adequacy of a log-linear association. In the first model, the UV radiation exposure variable was qualitative and categorized to obtain UV radiation based geographic zoning, which consisted of 10 groups of *Communes* ("deciles") D_k, k=1,…,10 with equal pediatric populations (0-14 years):

$$lnE(O_k) = \ln(E_k) + \sum_{h=1}^{10} \beta_h . X_h,$$

In which:

- $E(O_k)$ is the expected value of the observed number of cases (O_k) in decile D_k of the *Communes*, and E_k is the expected number of cases,

- X_h is an indicator variable with a value of 1 for decile D_h and 0 for the other deciles, and $ß_h$ is the corresponding regression coefficient.

For the second model, a semi-quantitative discrete UV radiation variable was built:

$$lnE(O_k) = \ln(E_k) + \alpha_0 + \beta . UV_k,$$

in which UV_k is the pediatric population weighted average value of the UV radiation exposure in decile D_k. In this model, e^{β} estimated the SIR variation with an increase of 1 UV radiation unit. In this study, one UV radiation unit is equal to an increase of 25 J/cm², which is about half of the UV radiation range for the *Communes*.

A value of the deviance/degrees of freedom ratio greater than 2 was considered to indicate an over-dispersed model. In the event of over-dispersion that was not explained by a more adequate model, a negative binomial error was used instead of the Poisson error.

Considering the shape of some of the associations between UV_k and the SIR, even when log-linearity was not formally rejected, a model with a segmented linear regression with one change point (τ) was also fitted to some observed CHM counts:

$$lnE(O_k) = \ln(E_k) + \alpha_1 + \beta . (UV_k - \tau)^+,$$

in which UV_k is the pediatric population weighted average value of the UV radiation exposure in the decile, D_k, $(UV_k - \tau)^+$ is the positive part of $(UV_k - \tau)$ which takes the value zero if $UV_k \leq \tau$ and $(UV_k - \tau)$ otherwise. In order to determine whether there was convincing evidence of a change point and determine the best change point, segmented linear regressions were fitted to the observations with values of τ every 2 J/cm² and the AIC criterion was used to identify the best model.

The regression models included no term of spatial autocorrelation even though exposures to UV are spatially correlated, since previous analyses of the data had not shown any spatial auto-correlation between CHM rates in France[28–30].

Analyses were performed by type and subtype of CHM, by age group and gender. The study had a statistical power of 80% for underlying exact SIR less than 0.85 or greater than 1.15 for most types of CHM with a two-sided Poisson test at the 5% level for a general pediatric population exposure frequency of 10%.

The stability of the results was first assessed by examining their consistency across three time periods (1990-1996, 1997-2003, 2004-2008) and five large geographic subdivisions of France (Paris area, North-West, North-East, South-East, South-West).

In order to account for potential confounding or effect modification, analyses were repeated after stratification by, or adjustment for, the urban status and socio-demographic characteristics of the *Communes* extracted from the 1999 census data. The French deprivation index FDep99[31] was defined as the first component (68% of the total variation) of a principal component analysis of four census variables: median income of the households, proportion of blue-collar workers, proportion of unemployed and proportion of baccalaureate (high school diploma) holders.

In a parallel analysis, the correlation between *Commune* sun exposure at birth and at diagnosis was estimated with data from two national population-based case-control studies conducted by the authors' team. The ESCALE study was conducted between 2003 and 2004 and included 763 AL cases and 1,681 controls [32]. The ESTELLE study was conducted between 2010 and 2011 and included 747 AL cases and 1,421 controls [33].

III.   Results

UV (UVA+UVB) radiation exposure varied between 85.5 and 137.8 J/cm² with a median of 100.2 J/cm². A clear north-south gradient of UV radiation exposure was observed, together with locally slightly higher UV radiation exposures in the Paris area and Alsace region (Figure 1).

The main subtypes of leukemia were acute lymphoblastic leukemia (ALL), which accounted for 82.0% of all AL and acute myeloid leukemia (AML), which accounted for 16.3% of all AL (Table 1). The lymphomas consisted in 58.7% non-Hodgkin's lymphoma (NHL) and 41.3% Hodgkin's lymphoma.

UV radiation exposure was positively associated with the incidence of AL (Table 2), with a significant log-linear trend. The association was limited to ALL, with a 9% increase in SIR (SIR=1.09;95%CI [1.03-1.14]) for an increase of 25 J/cm². A positive linear trend was found and was borderline significant for NHL, particularly the Burkitt subtype. However, the overall heterogeneity test for the ten deciles of exposure was clearly not significant (Table 3).

Age at diagnosis significantly interacted with UV radiation exposure (p=0.007). The association between UV radiation exposure and ALL was only observed for children aged less than 5 years (SIR=1.16;95%CI [1.08-1.25]) (Supplementary table A). For the children aged more than 5 years, the SIR was almost equal to 1 and not significant. In contrast, gender had no significant modifying effect (Supplementary table B).

The results were also heterogeneous across the three main subtypes of ALL (p=0.036). A positive and still very highly significant association only remained for PBC-ALL, the most common ALL subtype with 5,977 cases (Table 2). The modifying effect of age at diagnosis also remained significant for PBC-ALL (p=0.035) (Table 4). A positive linear trend, borderline significant, was found for the 10-14 years age group. However, the heterogeneity test was not significant and the shape of the association was quite different from that of the 0-4 years age group.

The association between UV radiation exposure and the incidence of PBC-ALL in young children did not seem to be linear over the whole range of UV radiation exposure since the SIR were significantly greater than 1 only in the last three UV radiation exposure deciles (Table 4). Threshold log-linear Poisson regressions were adjusted with various possible values of the threshold and the clearly bestfit with the data was obtained with a threshold value of 100 J/cm². The corresponding SIR was 1.24 (95%CI [1.14-1.36]) for a 25 J/cm² difference in UV exposure among *Communes* exposed to 100 J/cm² or more (Table 4 and Supplementary figure).

The associations observed between residential UV radiation exposure and PBC-ALL diagnosed before age 5 years in the three time periods (1990-1996, 1997-2003, 2004-2009) were very similar, and no modifying effect of time period on the association between UV radiation exposure and PBC-ALL diagnosed before age 5 years was observed (Table 5).

Analyzing this association across 5 large French regions (North-East, Paris area, North-West, South-West, South-East) showed that it was positive and significant in the South-East region (SIR = 1.25; 95%CI [1.07, 1.45]), where UV radiation exposure is both greater on average than in the other regions and more variable (Table 5). In the South-West and North-West, the association was positive but not statistically significant. The UV radiation exposure variability in the Paris area was so limited that it could not be considered separately. This was also practically the case for the North East region, where the population exposed to more than 100J/cm² was very small (2.7%). However, when the South-East was excluded, the association between PBC-ALL diagnosed before age 5 years and UV radiation exposure was positive and significant (SIR: 1.46; 95%CI [1.14-1.87] for a 25-unit increase in UV above 100 J/cm²). Overall, there was no statistically significant modifying effect of the UV radiation PBC-ALL association by region (p=0.63).

A significant log-linear trend between PBC-ALL incidence and a French deprivation index (Fdep) was observed, with a slightly higher incidence of PBC-ALL before age 5 years in less deprived *Communes* (p=0.03). No modifying or confounding effect of this variable on the association between *Commune* UV radiation exposure and PBC-ALL diagnosed before age 5 years was evidenced. Sensitivity analyses on the South East of France, the region with the highest and most variable UV radiation exposure, which was also the region where the Fdep was most associated with PBC-ALL, did not show any modifying effect of Fdep on the association between UV radiation exposure and PBC-ALL (data not shown).

No association between PBC-ALL and urban status was observed (p=0.51). No modifying or confounding effect of urban status on the association between UV radiation exposure and PBC-ALL before age 5 years was observed (data not shown).

Considering the ESCALE and ESTELLE case-control data, a strong correlation (r) between the sun exposure of the *Commune* of residence of the controls at birth and that of their *Commune* of residence at inclusion in the study was found, especially for the youngest children (aged less than 5 years) (r = + 0.90 for ESCALE and ESTELLE).

IV.   Discussion

There was a positive association between the *Commune* spatial variability of UV radiation exposure and that of the incidence of PBC-ALL for the children aged less than 5 years in France for the period 1990-2009. No significant association was evidenced for the other CHM or at other ages. The association observed was the same for both genders, and was not modified by time period. No regional heterogeneity was observed. Stratification by, or adjustment for, a French deprivation index (*Fdep99*) and an urban unit variable did not significantly change the association between UV radiation exposure and the incidence of PBC-ALL in young children.

The power of the comparisons was evaluated *a priori* to be greater than 80% for SIR less than 0.85 or greater than 1.15 for most types of CHM, for a frequency of exposure of 10%. Even though multiple comparisons were performed by studying the association for each type of CHM, subtype of leukemia, age group, gender, and some potential confounding factors, the statistical significance level of the association and its consistency with respect to several stratifications do not suggest a random association.

The strengths of this study consist in the objectivity of the sun exposure data, available on a fine scale (*Communes*), and the exhaustiveness and high quality of the incidence data, and the long time period studied, which enabled large numbers of CHM cases to be studied by type and subtype. The population studied was relatively homogeneous and lived over a large area with a fairly wide distribution of UV radiation exposures.

Because of the very high spatial correlation between UVA and UVB, it was not possible to distinguish their associations with CHM.

Although the *Commune* UV radiation exposures were highly auto-correlated, an auto-correlated structure for the observed Poisson count was not considered relevant as the dependent variable was not spatially auto-correlated in any of the studies conducted in France. The small yearly variations in CHM incidence that had previously been observed[34] were taken into account in the estimates of the expected number of cases for each *Commune*.

As a result of the highly auto-correlated and smooth continuous spatial variation of *Commune* sun exposure, the sun exposure in the *Commune* of residence at inclusion in the study for the controls, was very closely correlated with that of the *Commune* of birth in two large population based case-control studies conducted by the authors' team on the same population of children (ESCALE: 2003-2004 and ESTELLE: 2010-2011). It is therefore unlikely that the findings of this study are dependent on considering the *Commune* at birth rather than the *Commune* at diagnosis. As a result, the association observed cannot be specifically related to a particular exposure time window for the children or their parents: before conception, during pregnancy, at birth, since birth, around diagnosis.

The present study detected a positive spatial correlation between a population exposure index, *Commune* sun exposure, and *Commune* PBC-ALL incidence in young children. Even though it is likely that this association does exist in the French pediatric population it may be either a direct individual association or, alternatively, reflect the effect of some other unknown individual or *Commune* characteristics, which are related to residential sun exposure and influence the incidence of this particular group of ALL. This is not the case for the increased incidence of children leukemia that has been observed in France in the close vicinity of nuclear power plants[35] or high voltage power lines[3]. Both increased incidences are very localized spatially and cannot explain the trend association found in this study.

Of the four studies published on the association between residential sun exposure and CHM, three used very different methods, populations or exposure variables, compared to those used herein. The

international study conducted by Musselman and Spector [22] found an inverse association between sun exposure and leukemia (lymphoid and acute non-lymphocytic leukemia), and, after adjusting on a socioeconomic index, no significant association with lymphoma, as in the present study. The exposure was assessed by the absolute latitude and by an annual solar radiation measurement based on NASA data. The study was conducted on a very large scale, in 57 countries (some partially covered), located on different continents. The Greek study [23] found an inverse association between NHL and individual sun exposure. The study was based on interviews and measured individual sun exposure in a country with a very different level of UV radiation exposure to that in France. In addition, the association reported was based on a limited number of subjects (87 NHL cases, 164 controls). A large Finnish study [25], which included 7,423 cases between 1964 and 2003, both adults and children, found, in a subgroup analysis, lower numbers of ALL in the dark season among children aged 2-4 years. The results were quite similar to those of the present study.

The study[24] most similar to the present study in terms of methods and power was a large Californian study, which included 10,476 cases and 207,568 controls. The exposure assessment was ecological and obtained from a geostatistical model that estimated ground level UV radiation from UV radiation measurement station data. An inverse relationship was found for ALL and Non-Hodgkin's lymphoma for children 0-5 years old. In contrast, the present study showed a significant positive association between sun exposure at diagnosis and PBC-ALL in young children (less than 5 years old) and no significant association with lymphoma. The Californian study analyzed sun exposure at birth and it may be that the correlation between sun exposure at birth and at diagnosis for the Californian children is not as strong as that observed in France. Furthermore, California has a different level of UV radiation exposure than France, as the maximum yearly average residential exposure to sun in France (137.8 J/cm2) is less than the first quartile of exposure in the Californian study (148.4 J/cm2). In addition, large fractions of the Californian population have different skin pigmentations and lifestyles. These may also contribute to explaining the different results. The Californian study recorded data on 'ethnicity' and the authors found a negative association with UV radiation exposure for children with Hispanic mothers (Hispanics were the largest ethnic group in the study) and African-American mothers, but not for children with Caucasian mothers. In the present study, no information on 'ethnicity' was available, but the majority of the French population is of Caucasian origin.

V.   Conclusion

This study suggests a positive geographic association between population residential UV radiation exposure greater than 100 J/cm² and the incidence of PBC-ALL, essentially for children under the age of 5 years. The systemic immune suppression induced by UV radiation may be a biological hypothesis for this finding. However, further ecological studies are necessary in order to replicate this result in other populations and investigate whether these findings are due to other spatially heterogeneous ecological factors that are associated with both population residential sun exposure and the particular subgroup of ALL. An additional question is whether there is an association between the individual UV radiation exposure of the child/mother/father and the risk of CHM. Investigation for such an association could only be conducted in the context of individual case-control studies and, possibly, sufficiently large cohort studies, which include precise individual information on exposure to sun and take into account individual childhood leukemia risk factors potentially associated with individual UV radiation exposure. Future studies should also address residential history, skin type and other factors that may be correlated with UV radiation exposure. Meanwhile, irrespective of whether the association is direct or not, it should be considered and taken into account in other spatial studies of the variability of childhood leukemia incidences rates in relation to other factors including environmental and behavioral factors.

VI.   Acknowledgments

VII. References

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Table 1: Distribution of childhood hematological malignancies, by age and gender (France 1990-2009)

	Boys				Girls				Both			
	0-4 years	5-9 years	10-14 years	Total	0-4 years	5-9 years	10-14 years	Total	0-4 years	5-9 years	10-14 years	Total
Leukemia												
ALL	2030	1321	832	4183	1746	953	561	3260	3776	2274	1393	7443
PBC-ALL	1765	849	498	3112	1630	792	443	2865	3395	1641	941	5977
B-ALL	72	115	63	250	27	39	19	85	99	154	82	335
T-ALL	164	345	262	771	72	111	92	275	236	456	354	1046
AML	351	171	226	748	343	175	210	728	694	346	436	1476
NOS AL	45	28	29	102	30	18	13	61	75	46	42	163
Total	2426	1520	1087	5033	2119	1146	784	4049	4545	2666	1871	9082
Lymphoma												
NHL	293	621	569	1483	132	216	260	608	425	837	829	2091
Lymphoblastic	75	121	145	341	44	40	62	146	119	161	207	487
Burkitt	167	357	239	763	46	85	59	190	213	442	298	953
Mature	51	143	184	378	42	90	137	269	93	233	321	647
HL	56	255	551	862	10	81	519	610	66	336	1070	1472
Total	349	876	1120	2345	142	297	779	1218	491	1173	1899	3563

AL: Acute leukemia; ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; PBC-ALL: precursor B-cell ALL ; B-ALL: Burkitt-cell Leukemia;T-ALL: T-cell ALL; AL NOS : Not otherwise specified AL; HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma

Table 2: Incidence of childhood leukemia (ages 0-14) by decile of UV radiation exposure (France, 1990-2009)

	Acute Leukemia (AL)				Acute lymphoblastic leukemia (ALL)				Acute myeloid leukemia (AML)			
UV radiation deciles (J/cm^2)	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
[85.5-90.3]	923	913.4	1.01	0.95-1.08	751	748.6	1	0.93-1.08	159	148.6	1.07	0.92-1.25
]90.3-94.1]	888	893.4	0.99	0.93-1.06	725	732.2	0.99	0.92-1.06	140	145.3	0.96	0.82-1.14
]94.1-97.2]	888	904	0.98	0.92-1.05	705	741.2	0.95	0.88-1.02	159	146.7	1.08	0.93-1.27
]97.2-99.1]	919	909.6	1.01	0.95-1.08	739	745.6	0.99	0.92-1.07	166	147.7	1.12	0.97-1.31
]99.1-100.2]	1082	1170.5	0.92	0.87-0.98	861	958.1	0.9	0.84-0.96	198	191.3	1.04	0.90-1.19
]100.2-100.9]	633	654.9	0.97	0.89-1.04	534	537.1	0.99	0.91-1.08	91	106.1	0.86	0.70-1.05
]100.9-105.5]	920	955.2	0.96	0.90-1.03	774	783.2	0.99	0.92-1.06	129	154.8	0.83	0.70-0.99
]105.5-109.3]	938	874.8	1.07	1.01-1.14	771	716.8	1.08	1.00-1.15	145	142.3	1.02	0.87-1.20
]109.3-123.9]	925	903.6	1.02	0.96-1.09	778	740.7	1.05	0.98-1.13	140	146.6	0.96	0.81-1.13
]123.9-137,8]	966	902.7	1.07	1.00-1.14	805	739.6	1.09	1.02-1.17	149	146.7	1.02	0.86-1.19
Total	9082	9082			7443	7443			1476	1476		
p for heterogeneity[a]			0.03				0.01				0.24	
p for departure from log-linearity[b]			0.11				0.09				0.19	
Trend by unit of 25 J/cm²			1.06	1.01-1.11			1.09	1.03-1.14			0.97	0.86-1.08

	Precursor B-cell ALL (PBC-ALL)				Burkitt-cell Leukemia (B-ALL)				T-cell ALL (T-ALL)			
UV radiation deciles	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
[85.5-90.3]	581	599.8	0.97	0.89-1.05	40	33.8	1.18	0.87-1.61	122	106.2	1.15	0.96-1.37
]90.3-94.1]	552	586.8	0.94	0.87-1.02	52	33.1	1.57	1.20-2.06	109	103.9	1.05	0.87-1.27
]94.1-97.2]	571	594.3	0.96	0.89-1.04	27	33.5	0.81	0.55-1.18	98	104.9	0.93	0.77-1.14
]97.2-99.1]	607	599.1	1.01	0.94-1.10	24	33.5	0.72	0.48-1.07	97	104.5	0.93	0.76-1.13
]99.1-100.2]	666	773.8	0.86	0.80-0.93	47	42.4	1.11	0.83-1.48	136	131	1.04	0.88-1.23
]100.2-100.9]	444	433	1.03	0.93-1.13	25	23.9	1.05	0.71-1.55	61	74.1	0.82	0.64-1.06
]100.9-105.5]	615	628.5	0.98	0.90-1.06	40	35.4	1.13	0.83-1.54	112	110.4	1.01	0.84-1.22
]105.5-109.3]	638	575.2	1.11	1.03-1.20	24	32.4	0.74	0.50-1.11	101	101	1.00	0.82-1.21
]109.3-123.9]	653	593.4	1.1	1.02-1.19	27	33.7	0.8	0.55-1.17	93	105.3	0.88	0.72-1.08
]123.9-137.8]	650	593.1	1.1	1.01-1.18	29	33.5	0.87	0.60-1.25	117	104.7	1.12	0.93-1.34
Total	5977	5977			335	335			1046	1046		
p for heterogeneity[a]			<0.0001				0.02				0.43	
p for departure from log-linearity[b]			0.31				0.06				0.34	
Trend by unit of 25 J/cm²			1.12	1.03-1.22			0.75	0.57-0.97			1.00	0.87-1.15

E = Expected number of cases; O = Observed number of cases; SIR and 95% CI = Standardized Incidence ratio and its 95% confidence interval
[a]p-value of the test for heterogeneity of the SIR observed across the 10 strata of UV radiation exposure; [b]p-value of the test for departure from log-linearity of the SIR

Table 3: Incidence of childhood lymphoma (ages 0-14) by decile of UV radiation exposure (France, 1990-2009)

	Lymphoma				Non-Hodgkin's lymphoma (NHL)				Hodgkin's lymphoma (HL)			
UV radiation deciles (J/cm^2)	O	E	**SIR**	95% CI	O	E	**SIR**	95% CI	O	E	SIR	95% CI
[85.5-90.3]	297	361.7	**0.82**	0.73-0.92	176	212.2	**0.83**	0.72-0.96	121	149.5	**0.81**	0.68-0.97
]90.3-94.1]	384	354.4	**1.08**	0.98-1.20	221	207.7	**1.06**	0.93-1.21	163	146.8	**1.11**	0.95-1.29
]94.1-97.2]	347	358.1	**0.97**	0.87-1.08	192	209.9	**0.91**	0.79-1.05	155	148.3	**1.05**	0.89-1.22
]97.2-99.1]	334	355.3	**0.94**	0.84-1.05	200	208.8	**0.96**	0.83-1.10	134	146.5	**0.91**	0.77-1.08
]99.1-100.2]	495	440.1	**1.12**	1.03-1.23	291	260.8	**1.12**	0.99-1.25	204	179.3	**1.14**	0.99-1.31
]100.2-100.9]	257	249.8	**1.03**	0.91-1.16	139	147.7	**0.94**	0.80-1.11	118	102.1	**1.16**	0.97-1.38
]100.9-105.5]	373	376.9	**0.99**	0.89-1.10	221	221.0	**1.00**	0.88-1.14	152	155.9	**0.98**	0.83-1.14
]105.5-109.3]	346	345.1	**1.00**	0.90-1.11	220	202.2	**1.09**	0.95-1.24	126	143.0	**0.88**	0.74-1.05
]109.3-123.9]	360	362.0	**0.99**	0.90-1.10	222	211.1	**1.05**	0.92-1.20	138	150.9	**0.91**	0.77-1.08
]123.9-137,8]	370	359.6	**1.03**	0.93-1.14	209	209.8	**1.00**	0.87-1.14	161	149.9	**1.07**	0.92-1.25
Total	3563	3563			2091	2091			1472	1472		
p for heterogeneity[a]			0.01				0.08				0.03	
p for departure from log-linearity[b]			0.28				0.09				0.26	
Trend by unit of 25 J/cm²			**1.05**	0.94-1.17			**1.06**	0.97-1.17			**1.02**	0.88-1.20
	Lymphoblastic-NHL				Mature-NHL				Burkitt-NHL			
UV radiation deciles (J/cm^2)	O	E	**SIR**	95% CI	O	E	**SIR**	95% CI	O	E	**SIR**	95% CI
[85.5-90.3]	32	49.3	**0.65**	0.46-0.92	60	65.8	**0.91**	0.71-1.17	83	96.6	**0.86**	0.69-1.07
]90.3-94.1]	61	48.3	**1.26**	0.98-1.62	73	64.4	**1.13**	0.90-1.43	87	94.5	**0.92**	0.75-1.14
]94.1-97.2]	49	48.8	**1.00**	0.76-1.33	60	65.1	**0.92**	0.72-1.19	83	95.5	**0.87**	0.70-1.08
]97.2-99.1]	45	48.6	**0.93**	0.69-1.24	55	64.6	**0.85**	0.65-1.11	100	95.2	**1.05**	0.86-1.28
]99.1-100.2]	70	60.9	**1.15**	0.91-1.45	86	80.1	**1.07**	0.87-1.33	134	119.3	**1.12**	0.95-1.33
]100.2-100.9]	30	34.4	**0.87**	0.61-1.25	44	45.4	**0.97**	0.72-1.30	65	67.6	**0.96**	0.75-1.23
]100.9-105.5]	54	51.5	**1.05**	0.80-1.37	65	68.4	**0.95**	0.75-1.21	101	100.7	**1.00**	0.83-1.22
]105.5-109.3]	47	47.1	**1.00**	0.75-1.33	78	62.7	**1.24**	1.00-1.55	95	92.0	**1.03**	0.84-1.26
]109.3-123.9]	56	49.2	**1.14**	0.88-1.48	68	65.5	**1.04**	0.82-1.32	98	96.0	**1.02**	0.84-1.24
]123.9-137,8]	43	48.8	**0.88**	0.65-1.19	58	65.1	**0.89**	0.69-1.15	107	95.5	**1.12**	0.93-1.35
Total	487	487			647	647			953	953		
p for heterogeneity[a]			0.12				0.48				0.55	
p for departure from log-linearity[b]			0.08				0.39				0.81	
Trend by unit of 25 J/cm²			**1.01**	0.83-1.23			**0.99**	0.83-1.18			**1.14**	0.99-1.31

E = Expected number of cases; O = Observed number of cases; SIR and 95% CI = Standardized Incidence ratio and its 95% confidence interval
[a]p-value of the test for heterogeneity of the SIR observed across the 10 strata of exposure to UV ; [b]p-value of the test for departure from log-linearity of the SIR

Table 4: Association between UV radiation exposure and incidence of PBC-ALL by age group at diagnosis (France, 1990-2009)

UV radiation deciles (J/cm²)	0-4 years old				5-9 years old				10-14 years old			
	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
[85.5-90.3]	336	337.7	**0.99**	0.89-1.11	166	166.0	**1.00**	0.86-1.16	79	96.1	**0.82**	0.66-1.02
]90.3-94.1]	309	330.0	**0.94**	0.84-1.05	165	162.4	**1.02**	0.87-1.18	78	94.3	**0.83**	0.66-1.03
]94.1-97.2]	320	334.6	**0.96**	0.86-1.07	158	164.5	**0.96**	0.82-1.12	93	95.2	**0.98**	0.80-1.20
]97.2-99.1]	330	341.4	**0.97**	0.87-1.08	177	164.2	**1.08**	0.93-1.25	100	93.5	**1.07**	0.88-1.30
]99.1-100.2]	387	454.0	**0.85**	0.77-0.94	179	206.4	**0.87**	0.75-1.00	100	113	**0.88**	0.73-1.07
]100.2-100.9]	245	251.1	**0.98**	0.86-1.11	121	117.3	**1.03**	0.86-1.23	78	64.6	**1.21**	0.97-1.51
]100.9-105.5]	343	355.4	**0.97**	0.87-1.07	174	173.3	**1.00**	0.87-1.17	98	99.8	**0.98**	0.81-1.20
]105.5-109.3]	360	325.5	**1.11**	1.00-1.23	171	158.2	**1.08**	0.93-1.26	107	91.6	**1.17**	0.97-1.41
]109.3-123.9]	371	331.8	**1.12**	1.01-1.24	171	164.9	**1.04**	0.89-1.20	111	96.8	**1.15**	0.95-1.38
]123.9-137.8]	394	333.6	**1.18**	1.07-1.30	159	163.7	**0.97**	0.83-1.13	97	95.8	**1.01**	0.83-1.24
Total	3395	3395			1641	1641			941	941		
Heterogeneity p^a	0.0002				0.68				0.08			
Departure from log-linearity p^b	0.11				0.58				0.16			
Trend by unit of 25 J/cm²			**1.18**	**1.10-1.27**			**1.00**	**0.90-1.12**			**1.15**	**1.00-1.32**
Trend with threshold ^{c}			**1.24**	**1.14-1.36**								

E = Expected number of cases; O = Observed number of cases; SIR and 95% CI = Standardized Incidence ratio and its 95% confidence interval

[a]p-value of the test for heterogeneity of the SIR observed across the 10 strata of UV radiation exposure; [b]p-value of the test for departure from log-linearity of the SIR; [c]Trend with threshold: the threshold value which achieved the best fit to the data was 100 J/cm², the UVT variable is therefore the excess of UV radiation (in units of 25 J/cm²) above 100 J/cm², that is: UVT = 0 if UV ≤ 100 J/cm², UVT = (UV-100)/25 if UV ≥ 100 J/cm²

Table 5: Association between UV radiation exposure and incidence of PBC-ALL diagnosed before age 5 years in France 1990-2009, by time period and in 5 French regions

Variable	Strata	Min[a]	P10[a]	Median[a]	P90[a]	Max[a]	% pop (<5 years old) >100 J/cm²	O	E	SIR	95% CI
Periods	1990-1996	85.5	90.3	100.0	123.4	137.8	50.0	1176	1176	**1.20**	1.03-1.39
	1997-2003	85.5	90.4	100.2	123.6	137.8	51.0	1145	1145	**1.29**	1.11-1.49
	2004-2009	85.5	90.5	100.2	123.6	137.8	51.7	1074	1074	**1.24**	1.06-1.45
Geographic areas	South-East	93.8	103.5	116.5	130.8	137.8	96.0	852	784.5	**1.25**	1.07-1.45
	South-West	96.9	103.2	109.2	113.7	123.7	97.5	426	394.8	**1.67**	0.88-3.20
	Paris area[b]	97.3	99.1	100.2	100.9	101.7	54.8			-	
	North-West	88.2	93.0	97.6	104.4	117.8	26.3	685	682.5	**1.12**	0.59-2.11
	North-East	85.5	88.7	91.2	98.1	112.1	2.7	800	828.2	**0.29**	0.003-24.53
Overall association	France 1990-2009	85.5	90.3	100.2	123.5	137.8	50.9	3395	3395	**1.24**	1.14-1.36

O = Observed number of cases; E = expected number of cases; SIR = Estimated trend in SIR by unit of a 25 J/cm^2 above 100 J/cm^2 obtained from the slope of the adjusted Poisson regression of Observed over Expected number of cases as a linear function of *Commune* UVT exposure, with UVT = 0 if UV ≤ 100 J/cm^2, UVT = (UV- 100)/25 if UV ≥ 100 J/cm^2); [a] UV radiation distribution per stratum weighted by the population aged less than 5 years; [b] Paris was excluded because of the very low variability of the UV radiation distribution in that area
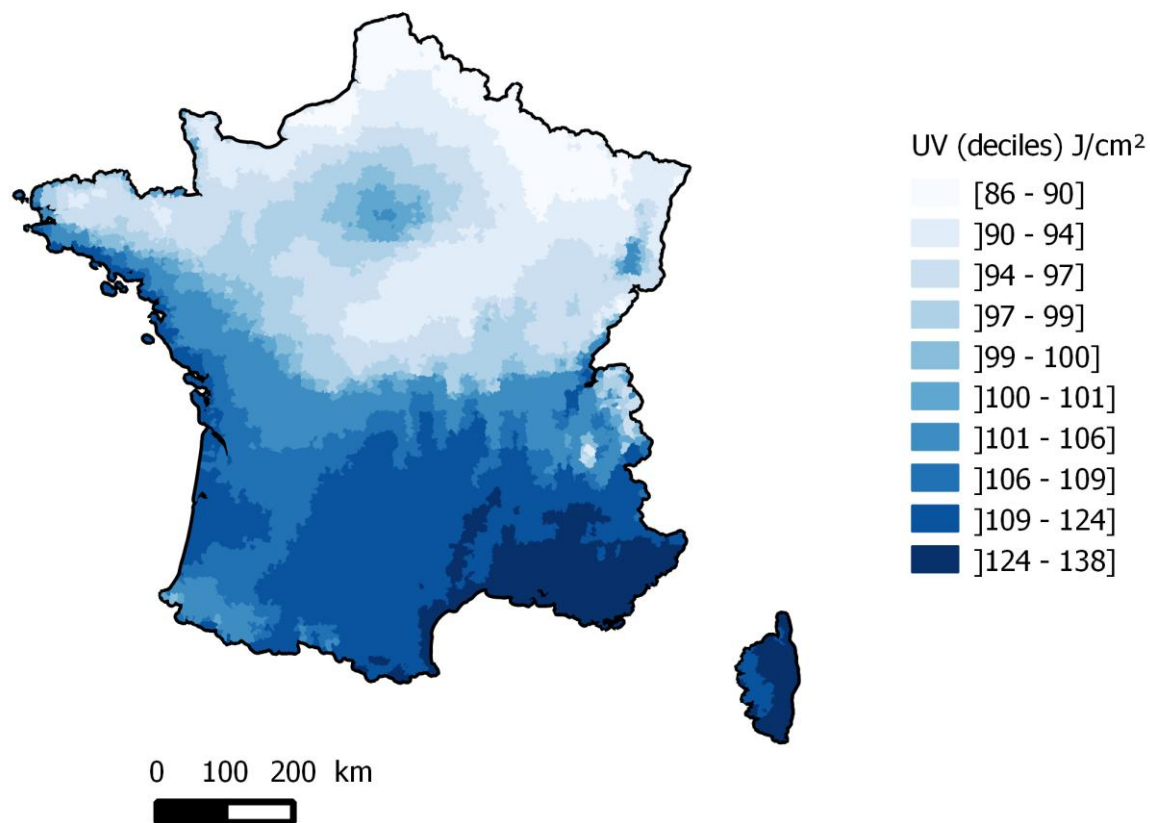
UV (deciles) J/cm²

[86 - 90]
]90 - 94]
]94 - 97]
]97 - 99]
]99 - 100]
]100 - 101]
]101 - 106]
]106 - 109]
]109 - 124]
]124 - 138]

0   100 200 km

Figure 1: UV radiation: spatial variations in France, 1988-2007 (J/cm²) [a]

[a] The 36,326 *Communes* in France

Supplementary table A: Association between UV radiation exposure and ALL incidence by age group at diagnosis (France, 1990-2009)

| UV radiation deciles (J/cm²)	0-4 years old				5-9 years old				10-14 years old			
	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
[85.5-90.3]	380	375.9	1.01	0.91-1.12	236	230.3	1.02	0.90-1.16	135	142.4	0.95	0.80-1.12
]90.3-94.1]	353	367.2	0.96	0.87-1.07	238	225.3	1.06	0.93-1.20	134	139.7	0.96	0.81-1.14
]94.1-97.2]	354	372.2	0.95	0.86-1.06	210	228.0	0.92	0.80-1.05	141	141.0	1.00	0.85-1.18
]97.2-99.1]	362	379.7	0.95	0.86-1.06	239	227.6	1.05	0.93-1.19	138	138.4	1.00	0.84-1.18
]99.1-100.2]	442	504.8	0.88	0.80-0.96	261	285.7	0.91	0.81-1.03	158	167.7	0.94	0.81-1.10
]100.2-100.9]	265	279.2	0.95	0.84-1.07	159	162.4	0.98	0.84-1.14	110	95.5	1.15	0.96-1.39
]100.9-105.5]	380	395.2	0.96	0.87-1.06	243	240.1	1.01	0.89-1.15	151	147.9	1.02	0.87-1.20
]105.5-109.3]	399	361.9	1.10	1.00-1.22	224	219.2	1.02	0.90-1.17	148	135.7	1.09	0.93-1.28
]109.3-123.9]	403	368.9	1.09	0.99-1.20	230	228.5	1.01	0.88-1.15	145	143.2	1.01	0.86-1.19
]123.9-137.8]	438	371.0	1.18	1.08-1.30	234	227.0	1.03	0.91-1.17	133	141.6	0.94	0.79-1.11
Total	3776	3776			2274	2274			1393	1393		
Heterogeneity p=[a]		0.0004				0.79				0.83		
Departure from log-linearity p=[b]		0.12				0.71				0.76		
Trend by unit of 25 J/cm²			1.16	1.08-1.25			1.02	0.93-1.11			1.00	0.89-1.13

E = Expected number of cases; O = Observed number of cases; SIR and 95% CI = Standardized Incidence ratio and its 95% confidence interval; [a]p-value of the test for heterogeneity of the SIR observed across the 10 strata of UV radiation exposure; [b]p-value of the test for departure from log-linearity of the SIR

Supplementary table B: Association between UV radiation exposure and childhood ALL incidence by gender (France, 1990-2009)

UV radiation deciles	Boys				Girls			
	O	E	SIR	95% CI	O	E	SIR	95% CI
[85,5-90,3]	429	422.0	**1.02**	0.92-1.12	322	326.6	**0.99**	0.88-1.10
]90,3-94,1]	423	411.7	**1.03**	0.93-1.13	302	320.6	**0.94**	0.84-1.05
]94,1-97,2]	390	416.5	**0.94**	0.85-1.03	315	324.7	**0.97**	0.87-1.08
]97,2-99,1]	426	418.8	**1.02**	0.93-1.12	313	326.8	**0.96**	0.86-1.07
]99,1-100,2]	484	536.4	**0.90**	0.83-0.99	377	421.7	**0.89**	0.81-0.99
]100,2-100,9]	286	300.8	**0.95**	0.85-1.07	248	236.3	**1.05**	0.93-1.19
]100,9-105,5]	439	440.5	**1.00**	0.91-1.09	335	342.7	**0.98**	0.88-1.09
]105,5-109,3]	403	403.3	**1.00**	0.91-1.10	368	313.5	**1.17**	1.06-1.30
]109,3-123,9]	440	416.9	**1.06**	0.96-1.16	338	323.8	**1.04**	0.94-1.16
]123,9-137,8]	463	416.3	**1.11**	1.02-1.22	342	323.3	**1.06**	0.95-1.18
Total	4183	4183			3260	3260		
Heterogeneity p=[a]			0.10				0.03	
Departure from log-linearity p=[b]			0.30				0.10	
Trend by unit of 25 J/cm²			**1.08**	1.01-1.16			**1.09**	1.01-1.18

E = Expected number of cases; O = Observed number of cases; SIR and 95% CI = Standardized Incidence ratio and its 95% confidence interval; [a]p-value of the test for heterogeneity of the SIR observed across the 10 strata of UV radiation exposure; [b]p-value of the test for departure from log-linearity of the SIR

Supplementary figure: Standardized Incidence Ratio (SIR) of PBC-ALL diagnosed before age 5 years in France, 1990-2009, as a function of the UV radiation exposure of the *Commune* of residence at diagnosis
Observed SIR with 95% CI by UV radiation decile and SIR predicted from the fitted threshold linear model
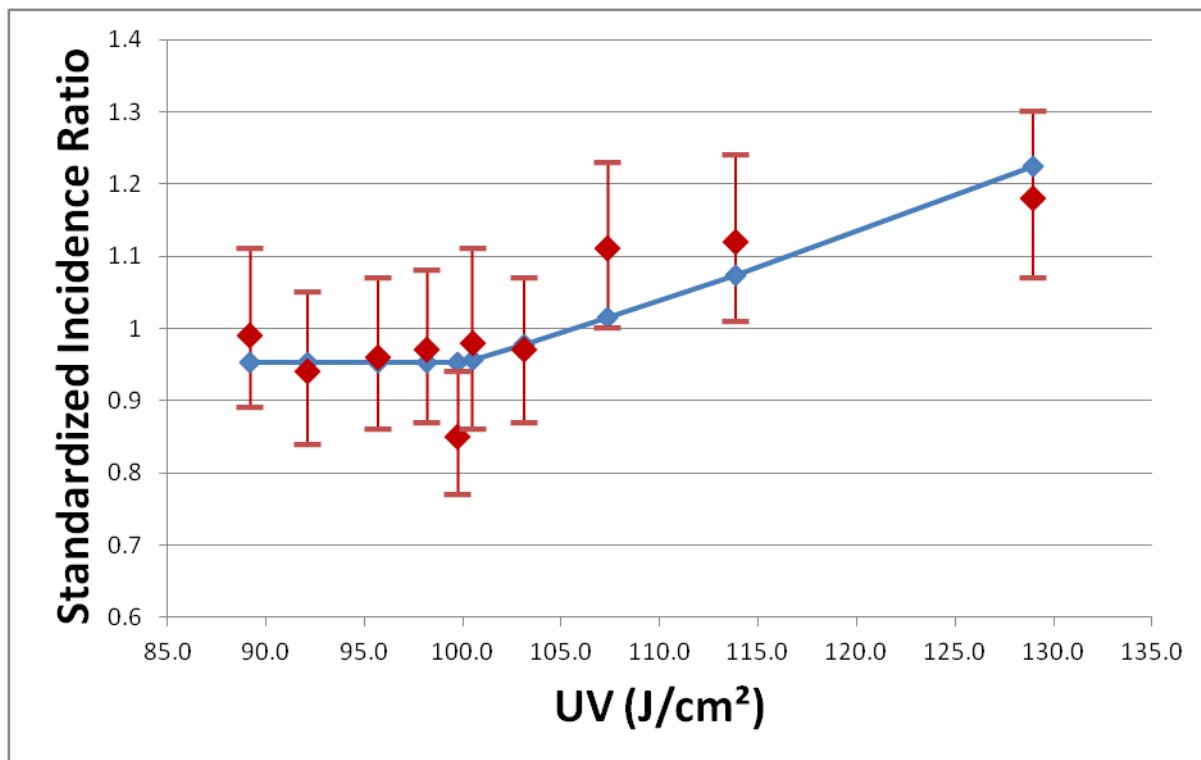
[a] Vertical bars: Observed SIR and 95% confidence limits
[b] Continuous line: SIR predicted by the model with the best fit (log-linear model with threshold at 100 J/cm^2)