

## APPENDICES

**Appendix A. Known and suspected risk factors for childhood cancers (CC) based on the literature-references: Summary of current evidence for postulated risk factors associated with childhood cancer.**

|                                                                                           | Known and suspected                            |                                                                                           | Causal criteria                                                 |                                                        |                                                                       | Likely/possible time window of effect (O) |          |            |         |                                                             |                                                     |
|-------------------------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------|----------|------------|---------|-------------------------------------------------------------|-----------------------------------------------------|
| Type of exposure                                                                          | Exposure Examples                              | Outcome Examples                                                                          | Relative risk estimate<br>+++ ≥2.0<br>++ ≥1.3<br><2.0<br>+ <1.3 | Consistency<br>++ ~100%<br>+ ≥50% <100%<br>± equivocal | Biological pathway<br>+++ identified;<br>++ suspected;<br>+ suggested | Pre/peri-conception                       | In-utero | Peri-natal | Infancy | Data on exposure currently available at IDCC (if collected) | Data collected by cohorts but not currently at IDCC |
| <b>Genetic – abnormal constitutional (&gt;10% of all childhood cancers)<sup>1-4</sup></b> | <b>Phenotypic abnormality</b>                  |                                                                                           |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                                                                                           | Neurofibromatosis (Autosomal Dominant)         | ALL, AML, Astrocytoma, juvenile myelomonocytic leukaemia, Neuroblastoma, Rhabdomyosarcoma | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some cohorts                                        |
|                                                                                           | Beckwith – Weidemann (AD; overgrowth syndrome) | Adrenocortical carcinoma, Hepatoblastoma, Neuroblastoma, Rhabdomyosarcoma, Wilms tumour   | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some cohorts                                        |
|                                                                                           | Fanconi anaemia                                | AML                                                                                       | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some                                                |

|                  | Known and suspected                              |                                                                               | Causal criteria                                                 |                                                        |                                                                       | Likely/possible time window of effect (O) |          |            |         |                                                             |                                                     |
|------------------|--------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------|----------|------------|---------|-------------------------------------------------------------|-----------------------------------------------------|
| Type of exposure | Exposure Examples                                | Outcome Examples                                                              | Relative risk estimate<br>+++ ≥2.0<br>++ ≥1.3<br><2.0<br>+ <1.3 | Consistency<br>++ ~100%<br>+ ≥50% <100%<br>± equivocal | Biological pathway<br>+++ identified;<br>++ suspected;<br>+ suggested | Pre/peri-conception                       | In-utero | Peri-natal | Infancy | Data on exposure currently available at IDCC (if collected) | Data collected by cohorts but not currently at IDCC |
|                  | (Autosomal Recessive)                            |                                                                               |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             | cohorts                                             |
|                  | Ataxia telangiectasia (AR)                       | ALL, AML, Lymphoma                                                            | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some cohorts                                        |
|                  | Bloom syndrome (AR; growth retardation)          | AML, Lymphoma, Wilms                                                          | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some cohorts                                        |
|                  | Simpson Golabi Behmel syndrome (X-linked)        | Hepatoblastoma, Wilms                                                         | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some cohorts                                        |
|                  | Down syndrome (sporadic +21)                     | ALL, AML                                                                      | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | Yes                                                         | --                                                  |
|                  | Trisomy 18 (sporadic mosaic; growth retardation) | Hepatoblastoma                                                                | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | Yes                                                         | --                                                  |
|                  | <b>Familial predisposition</b>                   |                                                                               |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                  | Li- Fraumeni (AD)                                | ALL, AML, Astrocytoma, Lymphoma, Medulloblastoma, Soft tissue & bone sarcomas | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some cohorts                                        |
|                  | Turcot syndrome (AD)                             | Astrocytoma, Medulloblastoma                                                  | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | No                                                          | Some cohorts                                        |
|                  | Retinoblastoma                                   | Retinoblastoma,                                                               | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | Yes                                                         | --                                                  |

|                                               | Known and suspected                   |                                       | Causal criteria                                                 |                                                        |                                                                       | Likely/possible time window of effect (O) |          |            |         |                                                             |                                                     |
|-----------------------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------|----------|------------|---------|-------------------------------------------------------------|-----------------------------------------------------|
| Type of exposure                              | Exposure Examples                     | Outcome Examples                      | Relative risk estimate<br>+++ ≥2.0<br>++ ≥1.3<br><2.0<br>+ <1.3 | Consistency<br>++ ~100%<br>+ ≥50% <100%<br>± equivocal | Biological pathway<br>+++ identified;<br>++ suspected;<br>+ suggested | Pre/peri-conception                       | In-utero | Peri-natal | Infancy | Data on exposure currently available at IDCC (if collected) | Data collected by cohorts but not currently at IDCC |
|                                               | (AD)                                  | Osteosarcoma                          |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
| Genetic – normal constitutional <sup>4</sup>  | Gender (non-germ cell)                |                                       |                                                                 |                                                        |                                                                       | O                                         |          |            |         |                                                             |                                                     |
|                                               | Females (risk >2.0)                   | Thyroid                               | +++                                                             | ++                                                     | +                                                                     | O                                         |          |            | O       | Yes                                                         | --                                                  |
|                                               | Males(risk >2.0)                      | Burkitt lymphoma (endemic & sporadic) | +++                                                             | ++                                                     | +                                                                     | O                                         |          |            | O       | Yes                                                         | --                                                  |
|                                               | Ethnicity <sup>5,6</sup>              |                                       |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                                               | Caucasian                             | Ewing's sarcoma,                      | +++                                                             | ++                                                     | ++                                                                    | O                                         | O        | O          | O       | Yes                                                         | --                                                  |
|                                               |                                       | Melanoma <sup>7</sup>                 | +++                                                             | ++                                                     | ++                                                                    |                                           |          |            | O       |                                                             |                                                     |
|                                               | Hispanic                              | ALL                                   | +                                                               | +                                                      | +                                                                     | O                                         | O        | O          |         | Yes                                                         | --                                                  |
|                                               |                                       | Retinoblastoma (sporadic)             | +                                                               | +                                                      | +                                                                     | O                                         | O        | O          | O       |                                                             |                                                     |
|                                               | Low-penetrance alleles <sup>8</sup>   |                                       |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                                               |                                       | ALL <sup>9</sup>                      | +                                                               | +                                                      | +                                                                     | O                                         |          |            |         |                                                             |                                                     |
|                                               |                                       | Glioma <sup>10</sup>                  | +                                                               | +                                                      | +                                                                     | O                                         |          |            |         |                                                             |                                                     |
| Environmental exposures - direct <sup>4</sup> | Ionizing radiation <sup>4,11,12</sup> |                                       |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                                               | Radiotherapy                          | CNS, Osteosarcoma                     | +++                                                             | ++                                                     | +++                                                                   |                                           |          |            |         | No                                                          | Yes                                                 |
|                                               | Pelvimetry                            | ALL, AML                              | +                                                               | +                                                      | ++                                                                    |                                           | O        |            |         | Yes                                                         | --                                                  |
|                                               | CT/MRI scans                          | ALL, AML, CNS                         | +                                                               | ++                                                     | ++                                                                    |                                           |          | O          | O       | No                                                          | Yes                                                 |
|                                               | Low-dose                              | ALL, AML, NHL                         | ++                                                              | +                                                      | +                                                                     | O                                         | O        | O          | O       | No                                                          | Yes                                                 |

|                  | Known and suspected                                    |                                                                          | Causal criteria                                                 |                                                        |                                                                       | Likely/possible time window of effect (O) |          |            |         |                                                             |                                                     |
|------------------|--------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------|----------|------------|---------|-------------------------------------------------------------|-----------------------------------------------------|
| Type of exposure | Exposure Examples                                      | Outcome Examples                                                         | Relative risk estimate<br>+++ ≥2.0<br>++ ≥1.3<br><2.0<br>+ <1.3 | Consistency<br>++ ~100%<br>+ ≥50% <100%<br>± equivocal | Biological pathway<br>+++ identified;<br>++ suspected;<br>+ suggested | Pre/peri-conception                       | In-utero | Peri-natal | Infancy | Data on exposure currently available at IDCC (if collected) | Data collected by cohorts but not currently at IDCC |
|                  | environmental radon/gamma/nuclear establishments       |                                                                          |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                  | <b>Non-ionizing radiation</b>                          |                                                                          |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                  | Ultraviolet (A/B)                                      | Melanoma <sup>13</sup>                                                   | ++                                                              | ++                                                     | ++                                                                    |                                           |          |            | O       | No                                                          | Yes                                                 |
|                  | Electromagnetic fields <sup>14</sup>                   | ALL                                                                      | +                                                               | ++                                                     | NK                                                                    |                                           | O        | O          | O       | No                                                          | Yes                                                 |
|                  | <b>Prescription drugs</b> <sup>15</sup>                |                                                                          |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                  | Cytotoxic/chemotherapy                                 | AML/MDS, CNS, thyroid                                                    | +++                                                             | ++                                                     | +++                                                                   |                                           |          |            | O       | No                                                          | Yes                                                 |
|                  | Fertility drugs/IVF <sup>16-19</sup>                   | Total, ALL, AML, CNS, Retinoblastoma                                     | +                                                               | ±                                                      | +                                                                     | O                                         | O        |            |         | Yes                                                         | --                                                  |
|                  | <b>Other chemical exposures examples</b> <sup>12</sup> |                                                                          |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
|                  | Pesticides                                             | Total, ALL <sup>20</sup> , AML, Brain tumours <sup>21</sup> , NHL, Wilms | +                                                               | ±                                                      | +                                                                     | O                                         | O        | O          | O       | Yes                                                         | --                                                  |
|                  | Tobacco smoke <sup>22</sup>                            | AML, ALL                                                                 | +                                                               | ±                                                      | +                                                                     | O                                         | O        | O          | O       | Yes                                                         | --                                                  |
|                  | ↓Folate <sup>23</sup>                                  | ALL, neuroblastoma                                                       | +                                                               | ±                                                      | +                                                                     | O                                         | O        |            |         | Yes                                                         | --                                                  |
|                  | <b>Infections</b> <sup>4,24</sup>                      |                                                                          |                                                                 |                                                        |                                                                       |                                           |          | O          | O       |                                                             |                                                     |
|                  | EBV                                                    | Burkett (endemic and sporadic), CHL                                      | +++                                                             | ++                                                     | ++                                                                    |                                           | O        | O          | O       | No                                                          | No                                                  |

|                                                                                                                                                            | Known and suspected                                      |                            | Causal criteria                                                 |                                                        |                                                                       | Likely/possible time window of effect (O) |          |            |         |                                                             |                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------|-----------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------|----------|------------|---------|-------------------------------------------------------------|-----------------------------------------------------|
| Type of exposure                                                                                                                                           | Exposure Examples                                        | Outcome Examples           | Relative risk estimate<br>+++ ≥2.0<br>++ ≥1.3<br><2.0<br>+ <1.3 | Consistency<br>++ ~100%<br>+ ≥50% <100%<br>± equivocal | Biological pathway<br>+++ identified;<br>++ suspected;<br>+ suggested | Pre/peri-conception                       | In-utero | Peri-natal | Infancy | Data on exposure currently available at IDCC (if collected) | Data collected by cohorts but not currently at IDCC |
|                                                                                                                                                            | HIV                                                      | CHL/DLBCL/Kaposi's sarcoma | +++                                                             | ++                                                     | +++                                                                   |                                           | O        | O          | O       | No                                                          | No                                                  |
|                                                                                                                                                            | KSHV (HHV-8)                                             | Kaposi's sarcoma           | +++                                                             | ++                                                     | ++                                                                    |                                           | O        | O          | O       | No                                                          | No                                                  |
|                                                                                                                                                            |                                                          |                            |                                                                 |                                                        |                                                                       |                                           |          |            |         |                                                             |                                                     |
| Health related states or events that are (or could be) proxies for other things (some of which may be genetic and/ or directly environmental) <sup>4</sup> | High birthweight, LGA, (cf. overgrowth syndromes)        | Wilms                      | +++                                                             | ++                                                     | +++                                                                   | O                                         |          |            |         | Yes                                                         | --                                                  |
|                                                                                                                                                            |                                                          | ALL                        | +                                                               | ++                                                     | +                                                                     | O                                         | O        |            |         |                                                             |                                                     |
|                                                                                                                                                            |                                                          | AML                        | +                                                               | +                                                      | +                                                                     | O                                         | O        |            |         |                                                             |                                                     |
|                                                                                                                                                            | Low birthweight, SGA, (cf. growth retardation syndromes) | Hepatoblastoma             | +++                                                             | ++                                                     | ++                                                                    | O                                         |          |            |         | Yes                                                         | --                                                  |
|                                                                                                                                                            | Caesarean (elective) <sup>25</sup>                       | ALL                        | +                                                               | +                                                      | +                                                                     |                                           | O        | O          |         | Yes                                                         | --                                                  |
|                                                                                                                                                            | Atopic comorbidities                                     | ALL                        | +                                                               | ±                                                      | +                                                                     |                                           |          | O          | O       | Yes                                                         | --                                                  |
|                                                                                                                                                            | Breast fed                                               | ALL                        | +                                                               | ±                                                      | +                                                                     |                                           |          | O          | O       | Yes                                                         | --                                                  |
|                                                                                                                                                            | ↑ ↓maternal age & paternal age <sup>26,27</sup>          | ALL, AML, Wilms            | +                                                               | ±                                                      | +                                                                     | O                                         | O        |            |         | Yes                                                         | --                                                  |
|                                                                                                                                                            | Prior fetal loss <sup>28</sup>                           | ALL                        | +                                                               | ±                                                      | +                                                                     | O                                         | O        | O          |         | Yes                                                         | --                                                  |

IDCC: I4C International Data Coordinating Centre

**AL:** acute leukemia

**ALL:** acute lymphoblastic leukemia

**AML:** acute myeloid leukemia

**Brain tumors-** astrocytomas, other gliomas, embryonal tumors, ependymomas

**NHL:** Non-Hodgkin lymphoma   **HL:** Hodgkin lymphoma

## References for Appendix A

1. Postema, F. A. M. *et al.* Childhood tumours with a high probability of being part of a tumour predisposition syndrome; reason for referral for genetic consultation. *Eur. J. Cancer Oxf. Engl. 1990* **80**, 48–54 (2017).
2. Brodeur, G. M., Nichols, K. E., Plon, S. E., Schiffman, J. D. & Malkin, D. Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson Jr. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **23**, e1–e5 (2017).
3. Ripperger, T. *et al.* Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am. J. Med. Genet. A.* **173**, 1017–1037 (2017).
4. Roman, E., Lightfoot, T., Picton, S. & Kinsey, S. Childhood Cancers. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 1119–1153 (Oxford University Press, 2018).
5. Friedrich, P., Itriago, E., Rodriguez-Galindo, C. & Ribeiro, K. Racial and Ethnic Disparities in the Incidence of Pediatric Extracranial Embryonal Tumors. *JNCI J. Natl. Cancer Inst.* **109**, (2017).
6. Steliarova-Foucher, E. *et al.* International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol.* **18**, 719–731 (2017).
7. Armstrong, B., Vajdic, C. & Cust, A. Melanoma. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 1061–1087 (Oxford University Press, 2018).
8. Zhang, J. *et al.* Germline Mutations in Predisposition Genes in Pediatric Cancer. *N. Engl. J. Med.* (2015). doi:10.1056/NEJMoa1508054
9. Wiemels, J. L. *et al.* GWAS in childhood acute lymphoblastic leukemia reveals novel genetic associations at chromosomes 17q12 and 8q24.21. *Nat. Commun.* **9**, 286 (2018).
10. Kinnnersley, B., Houlston, R. S. & Bondy, M. L. Genome-Wide Association Studies in Glioma. *Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol.* **27**, 418–428 (2018).
11. Berrington de Gonzalez, A., Bouville, A., Rajaraman, P. & Schubauer-Berigan, M. Ionizing Radiation. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 227–258 (Oxford University Press, 2018).
12. Linet, M., Morton, L., Devesa, S. & Dores, G. M. Leukaemias. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 715–744 (Oxford University Press, 2018).
13. Saiyed, F. K., Hamilton, E. C. & Austin, M. T. Pediatric melanoma: incidence, treatment, and prognosis. *Pediatr. Health Med. Ther.* **8**, 39–45 (2017).
14. Feychting, M. & Schüz, J. Electromagnetic Fields. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 227–258 (Oxford University Press, 2018).

15. Bradley, M., O'Rorke, M., Cooper, J., Friis, S. & Habel, L. Pharmaceutical drugs other than hormones. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 411–431 (Oxford University Press, 2018).
16. Wainstock, T. *et al.* Fertility treatments and pediatric neoplasms of the offspring: results of a population-based cohort with a median follow-up of 10 years. *Am. J. Obstet. Gynecol.* **216**, 314.e1–314.e14 (2017).
17. Dommering, C. J., van der Hout, A. H., Meijers-Heijboer, H., Marees, T. & Moll, A. C. IVF and retinoblastoma revisited. *Fertil. Steril.* **97**, 79–81 (2012).
18. Reigstad, M. M., Oldereid, N. B., Omland, A. K. & Storeng, R. Literature review on cancer risk in children born after fertility treatment suggests increased risk of haematological cancers. *Acta Paediatr. Oslo Nor.* **106**, 698–709 (2017).
19. Williams, C. L. *et al.* Cancer risk in children born after donor ART. *Hum. Reprod. Oxf. Engl.* **33**, 140–146 (2018).
20. Gunier, R. B. *et al.* A task-based assessment of parental occupational exposure to pesticides and childhood acute lymphoblastic leukemia. *Environ. Res.* **156**, 57–62 (2017).
21. Van Maele-Fabry, G., Gamet-Payrastre, L. & Lison, D. Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: A systematic review and meta-analysis. *Environ. Int.* **106**, 69–90 (2017).
22. Thun, M. & Freedman, N. D. Tobacco. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 185–212 (Oxford University Press, 2018).
23. Dessypris, N. *et al.* Association of maternal and index child's diet with subsequent leukemia risk: A systematic review and meta analysis. *Cancer Epidemiol.* **47**, 64–75 (2017).
24. Franceschi, S., El-Serag, H., Forman, D., Newton, R. & Plummer, M. Infectious agents. in *Cancer Epidemiology and Prevention* (eds. Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 433–460 (Oxford University Press, 2018).
25. Wang, R. *et al.* Cesarean Section and Risk of Childhood Acute Lymphoblastic Leukemia in a Population-Based, Record-Linkage Study in California. *Am. J. Epidemiol.* **185**, 96–105 (2017).
26. Marcotte, E. L. *et al.* Parental Age and Risk of Infant Leukaemia: A Pooled Analysis. *Paediatr. Perinat. Epidemiol.* **31**, 563–572 (2017).
27. Contreras, Z. A. *et al.* Parental age and childhood cancer risk: A Danish population-based registry study. *Cancer Epidemiol.* **49**, 202–215 (2017).
28. Karalexi, M. A. *et al.* Maternal fetal loss history and increased acute leukemia subtype risk in subsequent offspring: a systematic review and meta-analysis. *Cancer Causes Control CCC* **28**, 599–624 (2017).

## **Appendix B**

### **Ethics Committee reviews and approvals**

#### **1. ALSPAC**

- Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.
- Sharing and pooling of de-identified ALSPAC cohort data approved by the ALSPAC Executive Committee (application number B0681).

**2. CPP:** Data from the CPP are publicly available with identifying information removed.

#### **3. DNBC**

- Participants in the DNBC provided written informed consent on behalf of their children. The Regional Scientific Ethics Committee for the municipalities of Copenhagen and Frederiksberg approved the overall DNBC study protocols (case no: (KF) 01-471/94).
- A Data Processor Agreement between I4C and Statens Serum Institut covers the processing of data for the current article, which has also been approved by the DNBC Scientific and Administrative Committee. Sharing of de-identified data for pooling in the I4C was approved by the DNBC Scientific Committee at the Statens Serum Institut.

**4. JPS:** Pooling of JPS data with the I4C, with all identifiers removed, was approved by the institutional review board (Helsinki Committee) of Hadassah University Hospital.

#### **5. MoBa**

- Participation in MoBa is based on informed consent. MoBa is approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics South East.
- The current sub-study in I4C, including linkage with the Cancer Registry of Norway, is approved by the Regional Committee for Medical and Health Research Ethics South East.

#### **6. TIHS**

- Parents in the Tasmanian Infant Health Survey (TIHS) provided written consent on behalf of their children.

- Participation of the TIHS in the I4C was approved by the Southern Tasmanian Human Ethics

Research

Committee

## Appendix C

### Six key steps for submission of new proposals and data access for I4C

- 1 Investigator discusses research proposal with a member of the I4C Steering Committee [SC]
- 2 Research proposal is further developed and outlined in the I4C-specific **Concept Proposal Form**
- 3 Proposal is circulated to all members of the I4C SC
- 4 Proposal is discussed by SC (opportunity for Investigator or a Representative to present proposal) who identify any issues or concerns in terms of the scientific content, methodology or resources. Feedback to the Investigator is then provided by a member of the SC.
- 5 Once concerns or issues have been adequately addressed, the I4C SC grants approval for proposal to be undertaken under the I4C umbrella
- 6 Agreement (usually a Memorandum Of Understanding or Data Transfer Agreement) is set up between IDCC and Investigator that outlines the use and sharing of required data.

## I4C Concept Proposal Form

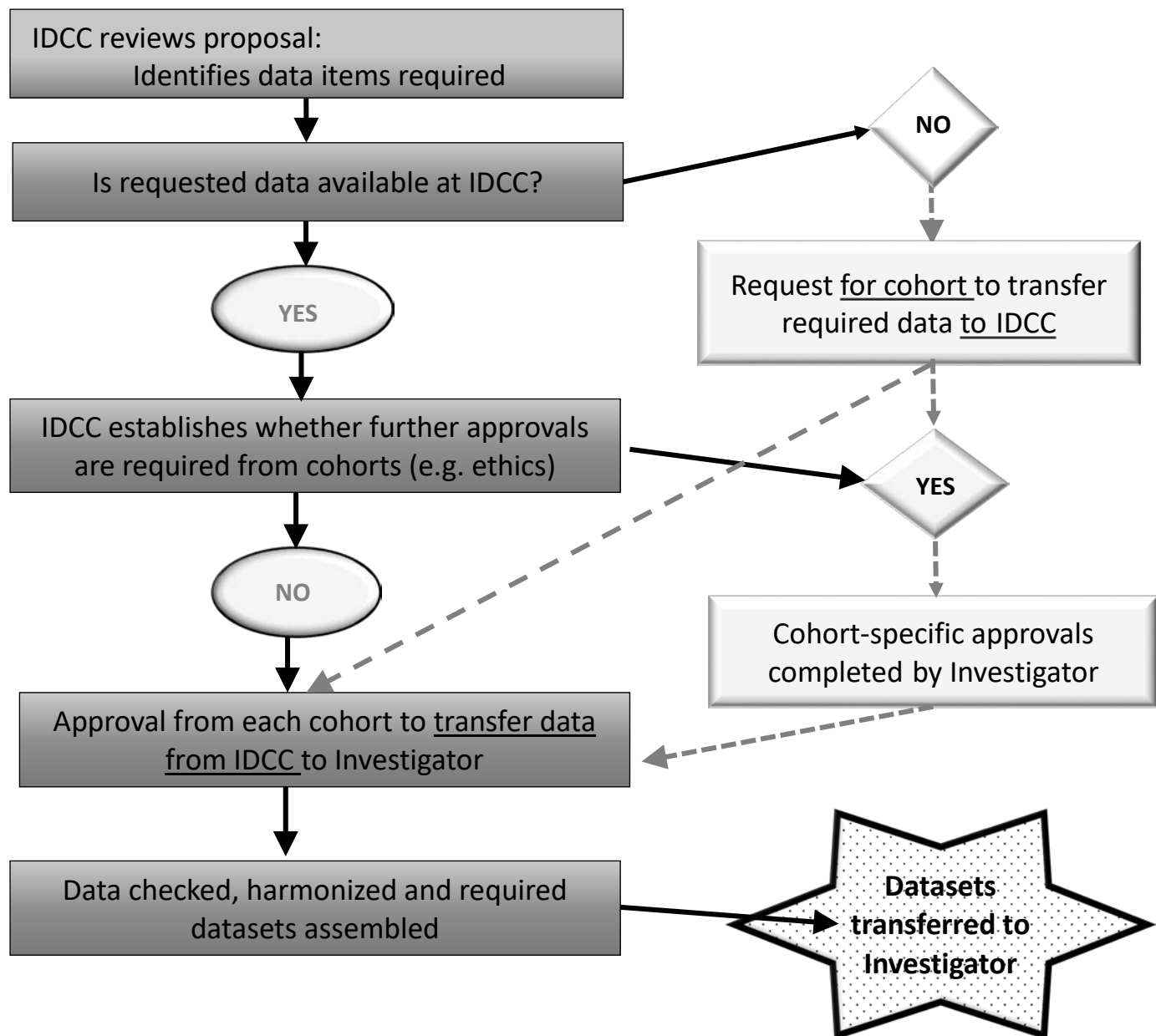
|                                                                                                                                     |                                                                                                                                                                                                                                                               |             |
|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| <b>International Childhood Cancer Cohort Consortium (I4C)</b><br><b>CONCEPT PROPOSAL FORM</b>                                       |                                                                                                                                                                                                                                                               |             |
| <b>Title:</b>                                                                                                                       |                                                                                                                                                                                                                                                               |             |
| <b>Type of Study:</b>                                                                                                               |                                                                                                                                                                                                                                                               |             |
| <b>Lead Investigator for Project</b><br>Name:<br>Institution:<br>Address:<br>Phone:<br>Fax:<br>E-mail:                              | <b>Sponsoring I4C Principal Investigator</b><br>Name:<br>Institution:<br>Address:<br>Phone:<br>Fax:<br>E-mail:                                                                                                                                                |             |
| <b>Additional Participating Sites to the Total Collaboration</b>                                                                    |                                                                                                                                                                                                                                                               |             |
| <b>Institution and Affiliation</b><br>1.<br>2.<br>3.<br>4.<br>5.<br>6.<br>7.<br>8.<br>(Continue as needed)                          | <b>Co-Investigator</b>                                                                                                                                                                                                                                        | <b>Role</b> |
| Please attach a <b>written description</b> of the proposed study, not to exceed 3 pages, with the following sections:               |                                                                                                                                                                                                                                                               |             |
| 1. Title<br>2. Objectives or Specific Aims<br>3. Background<br>4. Study Population<br>5. Human Subjects (list any potential issues) | 6. Study Design<br>7. Statistical Considerations<br>8. Significance and Future Directions<br>9. Utilization of I4C Resources<br>10. Funding of project.<br>11. Timeline for project<br>12. How the derived new data variable will be contributed to I4C study |             |

Additional comments

The **I4C Concept Proposal Form** is found in Appendix 2 of the ***I4C Policies and Procedures Manual*** and can be accessed from the **NIH I4C portal** at <https://communities.nci.nih.gov/i4c/I4C%20Policies/Forms/AllItems.aspx> or by contacting the IDCC ([gabriella.tikellis@mcri.edu.au](mailto:gabriella.tikellis@mcri.edu.au))

## Review and preparation of data for new I4C proposals from the IDCC perspective.

This process is usually undertaken in parallel by personnel at the IDCC as new proposals are being considered by the I4C Steering Committee.



## Appendix D: Harmonization table showing variables for birth weight and pesticide exposure

| FACTOR                                   | FACTOR DEFINITION                                                                                                                                                                                            | SUMMARY OF HARMONIZATION OUTCOME                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Age</b>                               | <ul style="list-style-type: none"> <li>Maternal age at time of index child's birth</li> <li>Paternal age any time during pregnancy</li> </ul>                                                                | <ul style="list-style-type: none"> <li>Data available in all six studies</li> <li>Continuous variable either directly recorded or computed from mother's date of birth and child's date of birth.</li> <li>Usually recorded as a discrete variable early in pregnancy.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Breastfeeding</b>                     | <ul style="list-style-type: none"> <li>Duration of breast feeding</li> </ul>                                                                                                                                 | <ul style="list-style-type: none"> <li>Data available for five of the six contributing cohorts.</li> <li>Data collected varied across studies: start/stop age, feeding method at each month of age.</li> <li>Harmonized to any breast feeding during the first six months of life.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Diabetes</b>                          | <ul style="list-style-type: none"> <li>History of diabetes prior to pregnancy</li> <li>Gestational diabetes</li> </ul>                                                                                       | <ul style="list-style-type: none"> <li>Data available in five of the six contributing studies.</li> <li>Variable harmonized into three categories: no diabetes, gestational diabetes, non-gestational diabetes.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Education</b>                         | Highest level of education attained by parents, respectively                                                                                                                                                 | <p>Diversity in education systems across cohorts (e.g. <i>ALSPAC: CSE, Vocational, O Level, A Level, Degree, Children in the UK tend to start school at age 4 and by law stay to the age of 16 [i.e. have 12 years schooling]</i>). Used several approaches such as completed high school, completed tertiary education.</p> <ul style="list-style-type: none"> <li>Given tertiary education not similarly defined across the six cohorts, final harmonized variable defined <i>as greater than 12 years of education</i>. After discussions with cohort Investigators it was decided that due to the differences in the education system in the UK, the ALSPC data could not be harmonized to align with the remaining five cohorts.</li> </ul> |
| <b>Exposure to pesticides (prenatal)</b> | <ul style="list-style-type: none"> <li>Residential use of weed killers, insecticides, fungicides</li> <li>Trimester of use</li> <li>Occupation exposure to pesticides, farm animals, organic dust</li> </ul> | <ul style="list-style-type: none"> <li>Maternal and paternal job codes during the pregnancy for five of the six contributing cohorts harmonized to ISCO-88 codes</li> <li>Exposure to pesticides and organic dust from occupation estimated using ALOHA + job exposure matrix</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Marital status</b>                    | Marital status of mother at time of recruitment                                                                                                                                                              | <ul style="list-style-type: none"> <li>Data available in all six studies</li> <li>Cohabiting very common in Nordic countries. Therefore, married and cohabiting combined into one variable.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Maternal adiposity</b>                | <ul style="list-style-type: none"> <li>Height</li> </ul>                                                                                                                                                     | <ul style="list-style-type: none"> <li>Data available in all six studies.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|                                              |                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>measures</b>                              | <ul style="list-style-type: none"> <li>• Pre-pregnancy weight</li> <li>• BMI: kg/m<sup>2</sup></li> <li>• Pregnancy weight change: maternal weight at time of birth minus pre-pregnancy weight</li> </ul>                                                                                                 | <ul style="list-style-type: none"> <li>• Self-reported height collected in early in pregnancy: continuous variable in cm, inches or meters. Harmonized to 'm' to allow for calculation of BMI.</li> <li>• Self-reported weight just before learnt of pregnancy or in early weeks: continuous variable in g, kg or lbs/ounces.</li> <li>• BMI computed from height and weight</li> <li>• Given many mothers reported overall weight loss during pregnancy, harmonization of variable allows various outcomes (e.g. weight gain only) to be used in analysis.</li> </ul> |
| <b>Maternal alcohol consumption</b>          | <ul style="list-style-type: none"> <li>• Alcohol consumption</li> <li>• Trimester/week of gestation consumed</li> <li>• Number of drinks per weeks</li> <li>• Type of alcohol consumed</li> </ul>                                                                                                         | <ul style="list-style-type: none"> <li>• Alcohol consumption not collected in CPP or JPS</li> <li>• Consumption of alcohol harmonized to '<i>any alcohol consumption during pregnancy</i>'.</li> <li>• Data available to look at trimester of alcohol consumption, frequency of consumption although units of alcohol will differ across cohorts.</li> </ul>                                                                                                                                                                                                           |
| <b>Maternal cigarette smoking (prenatal)</b> | <ul style="list-style-type: none"> <li>• Any smoking history</li> <li>• Current smoking status</li> <li>• Number cigarettes smoke per day</li> <li>• Weeks gestation</li> <li>• Brand/type cigarette</li> </ul>                                                                                           | <ul style="list-style-type: none"> <li>• Differences in the level of detail collected (e.g. across each trimester or reported by gestational week or just number of cigarettes) regarding maternal smoking during pregnancy</li> <li>• Smoking harmonized to 'any smoking' reported during pregnancy</li> <li>• Data available to look at smoking by trimester</li> </ul>                                                                                                                                                                                              |
| <b>Maternal infections during pregnancy</b>  | <ul style="list-style-type: none"> <li>• Gastrointestinal infection</li> <li>• Respiratory infection</li> <li>• Cold/Influenza</li> <li>• Bacterial/fungal/parasitic</li> <li>• Nephritis</li> <li>• Urinary tract</li> <li>• STI- gonorrhea, syphilis, venereal, genital herpes, thrush, etc.</li> </ul> | <ul style="list-style-type: none"> <li>• Various infections collected across six studies but common illnesses are few.</li> <li>• Working group currently examining how to harmonize types of illnesses.</li> </ul>                                                                                                                                                                                                                                                                                                                                                    |
| <b>Passive cigarette smoking (prenatal)</b>  | <ul style="list-style-type: none"> <li>• Partner smokes</li> <li>• Exposed to smoking at home or at work</li> <li>• Number of hours per week exposed</li> </ul>                                                                                                                                           | <ul style="list-style-type: none"> <li>• Various exposure scenarios: live with smoker/s, in same room as smokers, exposure at work.</li> <li>• Passive smoking harmonized as '<i>partner or others living in same house smoked during pregnancy</i>'. Current analysis limited to non-work environment but data available to include <i>at work</i> exposure.</li> </ul>                                                                                                                                                                                               |
| <b>Radiation exposure</b>                    | <ul style="list-style-type: none"> <li>• X-rays taken during pregnancy</li> <li>• Site where x-ray taken</li> <li>• Trimester x-ray taken</li> </ul>                                                                                                                                                      | <ul style="list-style-type: none"> <li>• Data available in four cohorts</li> <li>• Radiation exposure harmonized as <i>x-ray at any site</i> and <i>x-ray in the abdomen or pelvic area</i> given one study combined abdominal and pelvic site together.</li> </ul>                                                                                                                                                                                                                                                                                                    |
| <b>Reproductive</b>                          | <ul style="list-style-type: none"> <li>• Previous fetal loss (e.g. miscarriage,</li> </ul>                                                                                                                                                                                                                | <ul style="list-style-type: none"> <li>• Data available in all six studies.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

|                |                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>history</b> | abortion, stillborn), weeks gestation <ul style="list-style-type: none"> <li>• Parity (number of live/still births)</li> <li>• Birth order</li> </ul> | <ul style="list-style-type: none"> <li>• Weeks gestation at loss available in four cohorts.</li> <li>• Miscarriage defined as loss at &lt;20 weeks gestation and previous abortion, harmonized across studies.</li> <li>• Parity harmonized to live birth or live birth ≥20 weeks gestation or stillbirth</li> <li>• Birth order used to determine first versus later born children</li> </ul> |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## Appendix E: Biosamples collected prior to development of cancer across the

four cohorts contributing data to I4C.

|                           | ALSPAC | CPP | DNBC                   | MoBA                   | TIHS      |
|---------------------------|--------|-----|------------------------|------------------------|-----------|
| <b>PREGNANCY</b>          |        |     |                        |                        |           |
| <b>Blood</b>              | √      | X   | √                      | √ (and paternal)       | √         |
| <b>Buccal swabs</b>       | X      | X   | X                      | X                      | X         |
| <b>Hair</b>               | X      | X   | X                      | X                      | X         |
| <b>Saliva</b>             | X      | X   | X                      | X                      | X         |
| <b>Serum</b>              | √      | √   | √ (plasma)             | X                      | X         |
| <b>Toe nail clippings</b> | X      | X   | X                      | X                      | X         |
| <b>Urine</b>              | √      | X   | √                      | √                      | X         |
| <b>Vaginal swabs</b>      | X      | X   | X                      | X                      | X         |
| <b>Other</b>              | X      | X   | X                      | X                      | X         |
| <b>BIRTH</b>              |        |     |                        |                        |           |
| <b>Placenta</b>           | √      | X   | √                      | X                      | X         |
| <b>Meconium</b>           | X      | X   | X                      | X                      | X         |
| <b>Cord blood</b>         | √      | √   | √ (and mother's blood) | √ (and mother's blood) | √         |
| <b>Guthrie card</b>       | X      | X   | √                      | √                      | √         |
| <b>Serum</b>              | X      | √   |                        |                        | X         |
| <b>Other</b>              | X      | X   | X                      | X                      | X         |
| <b>POSTNATAL</b>          |        |     |                        |                        |           |
| <b>Breastmilk</b>         | X      | X   | X                      | X                      | X         |
| <b>Hair (CHILD)</b>       | √      | X   | X                      | X                      | X         |
| <b>Nails (CHILD)</b>      | √      | X   | X                      | X                      | X         |
| <b>Serum (MOTHER)</b>     | X      | √   | X                      | X                      | √ (child) |
| <b>Saliva (CHILD)</b>     | X      | X   | X                      | X                      | X         |
| <b>Milk teeth(CHILD)</b>  | √      | X   | X                      | √                      | X         |
| <b>Urine (CHILD)</b>      | X      | X   | X                      | X                      | X         |
| <b>Other</b>              | X      | X   | X                      | X                      | X         |

## **Appendix F: I4C Web-based data application**

The I4C Web-based data application is stored at MCRI's secure e-Research portal and allows the user to view all the variables within each dataset and to then select variables of interest through the 'build query' option. The dataset is then downloaded as a raw data file for use in other statistical programs. In addition, a do-file can also be downloaded which provides the coding responses for each variable extracted from the data dictionary (if provided) or questionnaires.

A summary of the process involved in selecting and downloading variables is provided below.

**STEP 1:** View the cohort datasets available from the "Home" tab and then click on the "Datasets" tab to view which datasets are accessible (based on permissions) to the user.

## I4C Cohorts

| Cohort                 | Full Title                                                                  | Country   | Records |
|------------------------|-----------------------------------------------------------------------------|-----------|---------|
| <a href="#">ALSPAC</a> | Avon Longitudinal Study of Pregnancy & Childhood                            | ALSPAC    | 15211   |
| <a href="#">CPBDDP</a> | China-US Collaborative Project on Birth Defects and Disabilities Prevention | China     | 0       |
| <a href="#">CPP</a>    | Collaborative Perinatal Project                                             | USA       | 59391   |
| <a href="#">DNBC</a>   | Danish National Birth Cohort                                                | Denmark   | 8664    |
| <a href="#">JPS</a>    | Jerusalem Perinatal Study                                                   | USA       | 92409   |
| <a href="#">MoBa</a>   | Norwegian Mother and Child Cohort Study                                     | Norway    | 0       |
| <a href="#">NCS</a>    | National Children's Study                                                   | USA       | 0       |
| <a href="#">TIHS</a>   | Tasmanian Infant Health Survey                                              | Australia | 10628   |

**STEP 2:** In the 'Build query' tab, select the variables of interest by clicking on the box adjacent to the variable.

**CPP Father Data** [- Hide variables](#)

☐ Select/Clear All
 

☐ person personid  
☐ family familyid  
☒ n5238 age of father of baby (yrs)  
☒ n5241 education husband or F.O.B. (yrs)

**ALSPAC Unit Records** [- Hide variables](#)

☐ Select/Clear All
 

☐ oid\_506a Unique pregnancy identifier for I4C project  
☐ A\_leukemia  
☐ kb010 Health of child in 1st months  
☒ d375 Age of PTNR  
☒ c666a Partners highest ed qualification

**TIHS Unit Records** [- Hide variables](#)

☐ Select/Clear All
 

☐ tihs\_cancers Number of cancer diagnoses
 ☐ tor\_id Tasmanian cancer registry ID

☒ A\_20 father's age
 ☒ A\_21 father's education

Then select the "Run Query" button



**STEP 3:** Download the dataset as a raw text file which can then be imported into a statistical package. Additionally, syntax file can also be downloaded to accompany the dataset.

| father_age_edu.txt - Notepad |      | RAW DATA |       |       |      |      |
|------------------------------|------|----------|-------|-------|------|------|
| File                         | Edit | Format   | View  | Help  |      |      |
| I4C_UID                      | d375 | c666a    | n5238 | n5241 | A_20 | A_21 |
| ALSPAC00003A                 | 40   | 2        | .     | .     | .    | .    |
| ALSPAC00005A                 | 38   | 5        | .     | .     | .    | .    |
| ALSPAC00006A                 | 30   | 2        | .     | .     | .    | .    |
| ALSPAC00007A                 | 34   | 5        | .     | .     | .    | .    |
| ALSPAC00012A                 | 37   | 5        | .     | .     | .    | .    |
| ALSPAC00016A                 | 33   | 4        | .     | .     | .    | .    |
| ALSPAC00017A                 | 24   | 4        | .     | .     | .    | .    |
| ALSPAC00018A                 | .    | .        | .     | .     | .    | .    |
| ALSPAC00019A                 | 32   | 4        | .     | .     | .    | .    |
| ALSPAC00020A                 | 25   | -1       | .     | .     | .    | .    |

#### SYNTAX FILE

/\* Variable labels: Dataset ALSPAC Unit Records \*/

label variable kz021 "Sex";

-1 "Not known"

1 "Male"

2 "Female"

## **Appendix G: Statistical methods and models used in analysis to date in the I4C**

Important statistical issues encountered and strategies developed to address such issues.

### **1. Accounting for different cohorts.**

Possible strategies: include a set of dummy variables, using the random-effects (Shared Frailty) cox model, stratifying by cohort and analyzing each cohort separately.

Ultimately, the method used will depend on the specifics of the analyses and the homogeneity across cohorts.

### **2. Dealing with missing data for risk factors**

Missing data includes information not collected or, if collected, some observations missing.

For all I4C analyses, data will be imputed only for information collected but missing for random subjects. Chained multiple imputation (MI) has been used to date and the value of 20 complete datasets was chosen based on our collective experience running MI. Cox regression is then performed separately on each imputation  $m = 1, \dots, 20$  and the results are pooled into a single multiple-imputation result. The “chained” method fills in missing values in multiple variables iteratively by using chained equations, a sequence of univariate imputation methods with fully conditional specification (FCS) of prediction equations. [Ref]

The predictor variables used for imputation are based on variables in the dataset that have the least amount of missing data.

### **3. Dealing with different lengths of follow-up of the contributing cohorts**

Cohorts currently contributing to the pooled dataset have various levels of maturity due to differences in follow-up times. Time to event analysis (Cox proportional hazard regression)

can handle the various number of years a child is at risk of cancer as well as the right-censored data. Alternatively we can censor patients at an earlier time point so that the cohorts have similar maturities relative to the censoring point.

#### **4. Examining confounding and effect-modification of postulated risk factors**

Controlling variables are entered into the regression model as a potential confounder, a potential effect-modifier, or an important covariate. A confounder is identified when its addition to the model (that previously contained only the exposure) changed the exposure coefficient by more than 15% in either direction. Effect-modifiers are covariates that have a statistically significant interaction with the exposure. If a covariate is an effect-modifier, then it cannot be a confounder. Variables that are neither a confounder nor an effect-modifier can still be included if there is a biologically plausible reason for keeping them in the model. Starting with all confounders in the model, we remove them one at a time if they are no longer confounders of the risk factor or the other covariates in the model. This method leaves a parsimonious multivariable model.

#### **5. Finding the correct scale for continuous covariates**

One of the assumptions underlying the use of Cox proportional hazards regression is that the scale of the continuous covariates must be linear in the log-hazard. If the relationship between the log-hazard and the covariate is not linear, the covariate is transformed to the correct scale. The method of fractional polynomials is used to check the scale.

## **6. Testing the proportional hazard assumption for Cox regression models.**

One method of testing the assumption is by plotting the log-hazards against the natural log of analysis time. If the plots appear to be parallel, then the assumption of proportional hazards is not violated. This is often the preferred method since, with large datasets, the global test using Schoenfeld residuals can have too much power and thus small deviations in the proportional hazard assumption are statistically significant. If the covariate hazards are not proportional, then we run the analysis where we include an interaction between the covariate and analysis time using a time-varying covariate approach.

## **Appendix H: Outline of the *I4C New Cohort Protocol Support Package***

The development of the ***I4C New Cohort Protocol Support package*** (NCPS) has stemmed from work conducted as part of the first pooling project of the I4C. The objective of the NCPS is to provide a description of the methodology used for the harmonization of questionnaire data from the six cohorts currently contributing data to the I4C pool (ALSPAC, CPP, DNBC, JPS, MoBa, TIHS) as well as work undertaken during the early planning years of the National Childrens Study (NCS).

The purpose of this package is to provide researchers with a standardized format for the collection of environmental exposure data that are important for examining the etiology of childhood cancer. This package may be a useful tool for new birth cohorts currently being planned or existing cohorts that may wish to join the pooling efforts of the I4C to examine important environmental risk factors associated with childhood cancers. The NCPS has been used by Investigators in Brazil and Japan.

The NCPS package comprises of 2 main parts: **1) An Excel Workbook** and **2) A Word document**.

**The Excel Workbook** comprises of a summary of data across five separate tabs:

- 1) Prenatal
- 2) Birth
- 3) Postnatal
- 4) 'Extra domains' (areas not examined extensively in the current contributing cohorts;  
e.g. physical activity during pregnancy)
- 5) Biospecimens

Each tab is categorized according to:

- **Core items** identified across the five contributing cohorts. These represent aspects of the specific domain that are common to at least five of the six contributing cohorts and constitutes the minimum dataset that any new cohort would be required to collect to be contribute data to the I4C pool.

- **Additional complementary data.** This data provides additional information seen as complementary to the 'core' dataset. The 'core' and 'additional complementary data' combined, would provide more comprehensive and detailed information on the specific variable.

- **Question label:** Each variable in the Excel spreadsheet is linked to the Word document through the Question Label code.

- **Validation documentation:** Provides references for the validation or use of the content included in each question.

*An example: Maternal smoking during pregnancy*

#### **CORE ITEMS**

1) Smoked **cigarettes** during pregnancy by trimester (weeks gestation)

2) Number of cigarettes smoked per day during each trimester

[categories created from initial pooling exercise]

0= type of smoking is not cigarettes; 1= 1-10 cigs/day; 2= 11-20cigs/day 3=21+ cigs/day

3) Recreational drug use during pregnancy [ALSPAC, DNBC, MoBa, NCS]

Smoked: marijuana, hashish, grass, cannabis

Taken: Amphetamines- ecstasy, speed; Cocaine/crack; Heroin

**ADDITIONAL COMPLEMENTARY DATA (includes source/cohort)**

Ask participants to supply package from tobacco product used

- 1) Include 3 months prior to finding out about pregnancy [ALSPAC, NCS]
- 2) Type of tobacco product used: cigarettes, pipe, others
- 3) Include smoking history for baby's father : Smoked in 3 months before pregnancy, stopped smoking during pregnancy. Weeks gestation when smoked
- 4) Inclusion of nicotine gum, patches, other [MoBa, DNBC, NCS]

**For recreational drugs:**

- 5) Weeks gestation when used
- 6) Include 3 months prior to finding out about pregnancy
- 7) Frequency of use

**QUESTION LABEL IN WORD DOCUMENT: SMK**

**VALIDATION**

Frank DA et al Cocaine use during pregnancy: prevalence and correlates. Pediatrics 1988;82:888-95

Comparison of interview data and urine samples indicate that 24% denied use of cocaine at time and were identified solely by urine assay.

**The Word document:** essentially takes each of the domains and formats them into questions that can be utilized in a study setting. The wording reflects the type of information that should be collected, whilst the responses are based on common formats and categories generated from the I4C cohorts currently contributing data.

**BLACK font** indicates the 'Core from Foundation cohorts' question

*Example:* **Have you taken any vitamin supplements during your pregnancy?**

**BLUE font** indicates the 'Additional complementary data'. Some 'Additional complementary data' has been added to the 'Core' part of the question

*Example:* **Have you taken any vitamin supplements** in the 3 months prior to finding out you were pregnant **or** during your pregnancy

The NCPS can be accessed from the **NIH I4C portal:**

<https://communities.nci.nih.gov/i4c/default.aspx>

**OR** by emailing the I4C International Data Coordinating Centre Project Manager at [gabriella.tikellis@mcri.edu.au](mailto:gabriella.tikellis@mcri.edu.au)