CC/2017/19

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Less than lifetime exposure to carcinogens – to incorporate margin of exposure for children

Issue

1. The COC has previously considered providing guidance on how to estimate the health risks to humans of acute, short-term or less than lifetime (LTL) exposures to genotoxic and non-genotoxic carcinogens. This links with the topic on the horizon scan list of the margin of exposure to children.

2. This paper presents an up to date overview of the topic area as a whole, to enable to Committee to consider how best to provide advice in this area.

Introduction

3. A broad definition of LTL exposures is ‘any exposure that is not continuous daily exposure, i.e., short-term, intermediate, and intermittent exposures, or a combination thereof’ (Felter et al., 2011). Examples could include exposures on every other day throughout the year, a few times a year, and a single peak exposure, any of which may occur during certain life-stages (Gerats et al., 2016).

4. Standard animal toxicity studies that form the basis of chronic health-based guidance values, e.g. acceptable or tolerable daily intake (ADI or TDI), are generally based on daily dosing schemes. These however, do not mirror human LTL exposure profiles and the question therefore arises as to whether such intermittent or fluctuating exposure to a chemical poses a health risk to exposed individuals and, in particular, potentially sensitive sub-groups such as infants and children (Gerats et al., 2016).

5. Early-life exposure can also be considered a specific subtype of LTL exposure (Felter et al., 2015).

Literature search strategy

6. A literature search was performed by the National Centre for Environmental Toxicology at WRc (NCET at WRc) and IEH-Consulting Ltd. (IEH-C) (NCET at WRc/IEH-C) under contract to PHE on 01/09/2017, as described in Annex A.

Background to previous COC discussions

7. The Committee has considered the issue of LTL exposure intermittently since 2007, and these discussions are summarised below for information.

8. In 2006, the Committee concluded that the acute T25 approach would not be useful for the potency ranking of single-exposure genotoxic carcinogens. Therefore, in 2007, three alternative papers were considered by the committee (CC/07/1).

9. Halmes et al. (2000) stated that conventional risk assessments are generally predicated on the assumption that cancer risk increases as a function of the cumulative carcinogen dose. For exposure to a carcinogen at a given rate, this would mean that the excess cancer risk is a function of the duration of exposure. The authors tested this assumption by comparing the tumour response in NTP stop-exposure studies with that from a standard 2-year study on the same carcinogen. In many cases, the response in the stop exposure study was greater than the response that would be predicted from the 2-year study. For those cases where it was possible to calculate equivalent averaging times for tumour/sites, the results suggested that exposures of 13 to 66 weeks were generally more effective in producing tumours than continuous long-term studies would predict.

10. With regards to the Halmes et al. (2000) paper, the Committee considered that the approach based on the concept of Haber's Law[1] was not useful for several reasons: it was unlikely that the data from stop-exposure studies of at least 13 weeks duration could be extrapolated to the exposure durations of concern (<10 days); the analysis contained tumour responses from some stop exposure studies that were not considered significant in the long-term NTP studies; and a simple linear relationship between duration of exposure and cancer risk from genotoxic carcinogens may not apply.

11. The second paper evaluated by the Committee was that of Bos et al. (2004). This was mainly a theoretical paper, which considered whether short-term exposure (1-10 days) to genotoxic carcinogens may contribute to tumour development and, if so, whether this contribution to cancer risk could be quantified. A pragmatic approach was proposed, based on the premise that tumour incidence is linearly related to the cumulative dose of a chemical and incorporated the principle of the Virtually Safe Dose (VSD) associated with an "acceptable" risk level. The approach then applied factors to scale up from low level exposure daily over 70 years to the dose which might be "acceptable" if exposure was only for 1 day, or 2-10 days.

12. The paper by Bos et al (2004) proposed a pragmatic approach to assessing the carcinogenic risk following short-term exposure to genotoxic carcinogens, using the premise that tumour incidence is linearly related to the cumulative dose of a chemical; this approach is not recommended by the COC. Members had a number

[1] toxicity (k) is related to the concentration of the toxic chemical (C) and the time of exposure (T) or $C \times T = k$

of criticisms of the proposed approach but suggested that it may be possible to adapt the method by using the MOE approach and that this might provide a pragmatic approach to the risk assessment of short-term exposures to genotoxic carcinogens, although there would be some associated degree of uncertainty.

13. The third paper evaluated by the Committee was that of Murdoch et al. (1992) which considered approaches to estimating the lifetime risk associated with intermittent or time-dependent exposure to carcinogenic substances. The **lifetime average daily dose** (LADD, the received dose divided equally over a lifetime) has been used in the USA to estimate the risk associated with short-term exposure. Murdoch et al (1992) used a mathematical approach to generate a **lifetime equivalent constant dose** (LECD), which gave the same lifetime risk as the actual time dependent exposure pattern. They stated that a comparison between the LECD and the LADD gives a measure of the accuracy of risk estimates based on the LADD and a measure of correcting such estimates. In some circumstances, use of a lifetime average daily dose would underestimate cancer risk by 2 to 5- fold. However, the authors also concluded that it is possible to place plausible upper bounds on the error in estimates of risk based on the LADD.

14. Members considered that the paper by Murdoch et al (1992) was a theoretical approach that involved a number of unproven assumptions which it had not been possible to test. Overall, it was not considered useful.

15. In 2012, the Committee reviewed a publication by Felter et al (2011) which reported findings from an ILSI/HESI workshop on LTL exposure to carcinogens, held in late 2009 (CC/2011/16). The output from the workshop was a framework for assessing LTL exposure to potential human carcinogens, with the approach described relying heavily on Haber's law or modifications thereof. Overall, the COC considered that, as general guidance, the ILSI/HESI framework was informative but there was concern that the underlying approach was directed towards the US approach to cancer risk assessment which is based on quantitative risk assessment from animal data. It was considered reasonable to use this as a supporting reference in a Guidance Statement, but it should not be considered for integration into UK risk assessment.

16. In 2015, two margin of exposure (MOE)-based evaluations that mirrored the staged threshold of toxicological concern (TTC) approach (described by Müller et al., 2006; Humfrey, 2007; EMA, 2010) that was beginning to be evaluated by some agencies, were discussed (van den Berg et al., 2014; Reeuwijk et al., 2014). These are described further in paragraphs 32 – 37.

17. During the COC's Horizon Scanning exercise in 2015, it was highlighted that the interpretation of MOEs for children has not been explicitly discussed by COC, JECFA or EFSA. Publications in the literature generally refer to MOEs of greater than 10,000 as being a low concern for all age groups; including children. However, it might be argued either that a higher MOE value should be used to allow for potentially greater vulnerability of young children, or that a smaller MOE could

represent a low concern in young children for short exposure periods, provided that the MOE is greater than 10,000 over a longer period.

18. At the COC horizon scan exercise in 2016 (CC/2016/12), the applicability of the margin of exposure approach (MOE) for children was highlighted as an important area for development, particularly in context of LTL exposure. It was felt that examples or a case study were required to aid discussion.

Risk characterisation of genotoxic and non-genotoxic carcinogens: MOE and uncertainty factor approach[2]

19. In G06, COC states that '*for carcinogens with genotoxic activity, in the absence of mechanistic data to suggest a threshold for genotoxicity, or carcinogens where no threshold for effect has been or can be identified, it is prudent to assume that no threshold for carcinogenicity exists'*. The MOE approach[3], developed and used by the European Food Safety Agency (EFSA), the World Health Organisation (WHO) and the International Life Sciences Institute (ILSI), amongst others (EFSA, 2005; JECFA 2005; O'Brien et al., 2006), is described as a way of prioritising and assisting with the communication of the risks associated with unavoidable exposure to genotoxic chemical carcinogens.

20. For a given chemical, the MOE is the numerical value obtained by dividing a point of departure (POD) on the dose response curve by the estimated human exposure to that chemical. The preferred POD is generally accepted to be the lower 95% confidence limit of the benchmark dose ($BMDL_{10}$), because the BMDL takes into account uncertainty regarding the shape of the dose-response relationship, within the observed dose range of carcinogenicity studies.

21. The MOE provides a relative indication of the level of human health concern but not an estimation of the actual cancer risk. The COC has proposed a banding system for MOE values for neoplastic effects, when based on the $BMDL_{10}$ from a chronic animal study using tumour incidence as the effect of concern. When other points of departure are used, for example if based on human data, the margin of exposure should be considered on a case-by-case basis.

<10,000: may be a concern

10,000 – 1,000,000: unlikely to be a concern

1,000,000: highly unlikely to be a concern

22. For non-genotoxic carcinogens where there is adequate evidence to support a threshold for carcinogenicity, i.e. the compound and metabolites are not DNA

[2] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/315883/Risk_characterisation_methods.pdf

[3] Also known as the "large assessment factor approach" in the REACH guidance.

reactive and there is an adequate evaluation of the mode of action (MOA) for tumours observed in animal studies and the applicability to humans, the COC considers that an approach based on the use of uncertainty factors should be adopted. Although risk characterisation based on a BMDL is preferred, it is recognised that often a NOAEL is used as the POD.

23. Application of an appropriate uncertainty factor (UFs) to the POD defines a health based guidance value (e.g. ADI, TDI) which represents a daily dose or exposure for humans that is considered to be without appreciable risk *over a lifetime*. UFs take into account uncertainties and variability with regard to both kinetic and dynamic differences between experimental animals and humans (factor 4 × 2.5 = 10), and within the human population (factor 3.2 × 3.2 = 10) (Renwick, 1993). Where exposures occur above the derived ADI or TDI, qualitative estimations of risk are made on a case-by-case basis by assessing the frequency, duration and extent by which the health based guidance value is exceeded, and the nature and dose-response relationship for carcinogenicity, or other relevant form of toxicity of the substance in question. In the absence of an ADI or TDI, the MOE, can be informative. Usually for non-genotoxic compounds, unless there are major gaps in the toxicological database, a MOE of 100 is considered sufficient to conclude that there is no health concern. This MOE covers the same uncertainties and variabilities as applied when defining a health based guidance value.

24. Some authoritative bodies (e.g. US EPA) recommend the estimation of cancer risk by low dose extrapolation of animal data when certain criteria apply: there are data to suggest a linear response below the POD, where human exposure or body burden is close to doses associated with precursor carcinogenic events and, when the data are insufficient to establish a MOE for a tumour site (US EPA, 2005). The COC does not recommend the use of this approach because the resultant cancer risk estimate has a degree of precision which does not reflect the uncertainties about the shape of the dose response curve orders of magnitude below the doses administered in animal studies. This was the reason for some of the concern over the Felter et al. (2011) paper.

How do we define a child for risk assessment purposes?

25. There are no universally-accepted definitions for early-life and/or childhood stages. In an OECD-wide survey to evaluate the methodologies and tools used to assess the risk of chemicals to children's health, the OECD (2013) highlighted a number of categories used by authoritative bodies worldwide to differentiate child-related age groups for risk assessment purposes. Commonly used terms include: "newborn," "infants," "toddlers," "children," "young children," "older children," "teens," "juvenile," "adolescent" and "youth", with age groups often being differentiated on a case-by-case basis according to the chemical and route of exposure being assessed. Current definitions tend to reflect a developmental life-stage rather than an exact chronological age, such as those described by Firestone et al. (2007):

- birth to 1 month
- 1 to < 6months
- 6 – 12 months
- 1 to < 2 years
- 2 to <3 years
- 3 to <6 years
- 6 to <11 years
- 11 to <16 years
- 16 to 21 years

Are children at greater risk *per se* than adults from exposure to carcinogens?

26. There is an increasing awareness amongst risk assessors of the potential health impacts associated with early-life and/or childhood exposures. Although regulatory approaches to chemical risk assessment are intended to be protective for all life stages, questions persist as to whether these are adequately protective for infants and children (Felter et al., 2015). As a consequence, risk assessors are being encouraged to consider a range of different aspects when performing assessments of chemicals posing risks for children; these particularly include consideration of child-specific exposures, toxicokinetics and toxicodynamics. In terms of the application of uncertainty factors, for non-carcinogenic and non-mutagenic substances those currently used (10 x 10) are considered adequate in safeguarding the whole population, including infants and children (Renwick, 2006). However, for each chemical in the risk assessment process, it should always be considered whether children are sufficiently protected or whether the application of an additional uncertainty factor is warranted. The use of additional factors is already a possible approach in current risk assessment practice, however such use should always be justified (RIVM, 2007).

27. In a review of the application of current risk assessment methods to early-life exposures, Felter et al. (2015) conclude that infants and children do not always have greater sensitivity than adults with regard to toxicant exposures. However, there are well-documented cases in which infants and children are more sensitive and include exposures to chloramphenicol and lead, and cases in which they are less sensitive which include exposure to aminoglycosides such as gentamicin. For most chemicals however, there are insufficient data to conclude of the relative sensitivity between infants, children and adults.

28. From a risk assessment perspective, infants, children and adults will have different exposure profiles resulting from a greater intake on a body weight basis for infants and children, and/or unique behaviours including breastfeeding, crawling, and hand/object to mouth behaviour. For some life-stages, a higher susceptibility may be driven primarily by exposure; for example, exposure related to migration of chemicals from packaging into infant formula and breast-milk bags (Neal-Kluever et al. 2014). During this life-stage, exposure can change quickly alongside rapid developmental changes and it is important that this is captured when defining age

categories (see section 20). In terms of risk characterisation, the toxicokinetic handling of a chemical may be impaired as the metabolic and renal capacity of neonates is not fully mature at birth; this is usually resolved by the age of 2 - 6 months. This may result in an adverse effect if a specific chemical is normally detoxified during metabolism, or a protective effect if metabolism normally produces a more toxic metabolite. Less information is available to assess toxicodynamic differences between infants, children, and adults, however concern is greatest for early infancy when permanent adverse effects are possible to skeletal tissue, central nervous system, immune and endocrine systems (Felter et al., 2015).

29. The US EPA (2005) lists the following factors that could contribute to early life-stage susceptibility:

- More frequent cell division during development can result in enhanced fixation of mutations due to the reduced time available for repair of DNA lesions, and clonal expansion of mutant cells gives a larger population of mutants (Slikker et al. 2004).

- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.

- Some components of the immune system are not fully functional during development (Holladay and Smialowicz, 2000; Holsapple et al. 2003).

- Hormonal systems operate at different levels during different life stages (Anderson et al. 2000).

- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life (Anderson et al., 2000; Birnbaum and Fenton, 2003; Fenton and Davis, 2002).

30. The WHO (2011) state that '*the timing of exposure to chemicals or other insults is critical in determining the consequences to children's health'*. The potential outcome of an exposure may differ depending on whether it is co-incident with windows of susceptibility; for children the window is broad, extending from pre-conception through to adolescence. For carcinogens, although cancers do not commonly occur in humans up to the age of around 20 years, there is evidence to show that children are more susceptible than adults to some carcinogenic substances, including certain chemicals (diethylstilbestrol) and various forms of radiation (X-rays) (for example see: Tomatis & Mohr, 1973; Ron et al, 1988; Birnbaum & Fenton, 2003). Exposure to these carcinogens prior to conception, during intrauterine life, or in early childhood may result in the development of cancer during later childhood or subsequent adult life (WHO, 2011).

31. For the majority of environmental exposures of humans to chemicals with the potential to increase the risk of cancer, evidence that exposure during the perinatal or postnatal period will lead to childhood or adulthood cancers is currently equivocal.

Potential MOE-based approaches to evaluate the risk of LTL exposure to carcinogens in adults and children

32. Several guidance documents supporting the EU legislative frameworks on chemical safety such as biocides, veterinary medicines, cosmetics and industrial chemicals, highlight the issue of LTL, however, clear-cut approaches on how to deal with fluctuating or intermittent exposure are lacking (SCCS,2012; EMA, 2010; ECHA, 2015; ECHA, 2012a; ECHA, 2012b; ECHA,2012c). A framework for risk assessment of *non-carcinogenic* effects upon short-duration and intermittent chemical exposure has recently been published (Haber et al., 2016). The framework presents an integrated, tiered approach that assists the user in identifying when existing toxicity reference values (TRVs) can be applied directly, and the adaptations needed to assess the acceptability of short-duration or intermittent exposure scenarios. TRVs based on exposure periods as similar as possible to the "actual" exposure periods are used and dose averaging applied under limited, specified conditions.

33. Van den Berg et al. (2014) calculated the safety of estragole from both long-term and short-term (1-2 weeks) exposure to fennel teas using an MOE approach. Fennel-based teas are traditionally used in many parts of Europe for the symptomatic treatment of digestive disorders and the relief of symptoms during inflammation of mucous membranes of the upper respiratory tract. Homemade fennel tea is also often used as a remedy for gastrointestinal complaints in infants and young children (Crotteau et al., 2006; Perry et al., 2011). However, fennel may contain active ingredients of concern such as estragole, which has been shown to be genotoxic and carcinogenic. A number of authors had previously calculated the MOE for estragole from daily consumption of fennel teas. In all cases, the MOEs have been below 10,000, indicating that there may be a concern and a priority for risk management (Miller, 1983; EFSA, 2009; Raffo et al., 2011).

34. Van den Berg *et al* (2014) measured the amount of estragole in 34 samples of fennel teas from various countries, including 4 fennel-based preparations specifically marketed for infant use. They calculated MOEs by comparing the previously calculated $BMDL_{10}$ values of 3.3-6.5 mg/kg bw/day for the induction of hepatocellular carcinomas in female mice with the estimated daily intakes of estragole resulting from the consumption of 1or 3 cups of fennel tea (4.8 or 14.3 µg respectively). MOEs obtained for adults were generally > 10,000, especially when one cup of fennel tea is used daily during a lifetime (75 years). As shown in Table 1, MOEs for use of 1 cup of fennel tea marketed for infants were generally <10,000 for ages 0 to 3 years, indicating a priority for risk management.

Table 1: MOEs relating to fennel intake from tea preparations specifically marketed for infants by age groups.

Age Group	MOE (range – 4 samples)
Infants 0 – 3 months	3,000 – 6,000 1,000 – 2,000 6,000 – 10,000 500 - 1000
Infants 3 – 6 months	4000 – 8000 1000 – 3000 8,000 – 20,000 700 – 1000
Infants 6 – 12 months	6,000 – 10,000 2,000 – 4,000 10,000 – 20,000 900 – 2,000
Toddlers 1 – 3 years	8,000 – 20,000 3,000 – 5,000 20,000 – 30,000 1,000 – 3,000

35. The authors state that although the calculated MOEs for life-time use for infants may cause concern, these may be overestimated, as home-made fennel-based teas are generally only used during periods of gastrointestinal complaints. Indeed, the European Medicines Agency had previously indicated that fennel-based teas should not be used for more than 2 weeks by adults and less than one week by children under the age of 12 years (EMA, 2008).

36. To assess the impact of taking intermittent and/or short-term exposure into account when calculating the magnitude of the calculated MOEs, van den Berg et al. (2014) applied the principles in Felter et al (2011) and assessed the potential risk of short-term estragole exposure during a period of one week (children) and two weeks (adults), on an estimated life expectancy of 75 years. Although the calculation was not shown, the authors state that the resulting MOE values were 3 orders of magnitude higher than those obtained when assuming lifetime daily use of fennel based tea. The authors concluded that the findings indicated low risk for human health from using fennel teas in the short-term.

37. Reeuwijk et al. (2014) analysed 50 herbal food supplements that claimed to reduce weight, for active pharmacological ingredients (APIs) that can be used for the treatment of obesity. A number of APIs were identified, including the laxative phenolphthalein, a suspected carcinogen, which was present in 10 samples. The authors carried out a risk assessment for the presence of phenolphthalein using a MOE approach. A $BMDL_{10}$ of 85 mg/kg bw/day was identified based on the induction

of hystiocytic sarcomas in B6C3F$_1$ male mice (NTP, 1996) and daily intakes of phenolphthalein from the herbal supplements taken over a lifetime were estimated. MOE values for four of the ten samples were in the range 96-220.

38. Reeuwijk et al. (2014) reasoned that herbal food supplements may only be used for relatively short periods of several weeks or months and that the principles in Felter et al. (2011) could be applied to assess the potential risk of short-term exposure on an estimated life expectancy of 75 years. The authors stated that this may result in MOE values 2 or 3 orders of magnitude higher than those obtained when assuming life-term (75 years) daily use of the supplements and, therefore, are of lower concern.

39. In terms of adopting the methodology employed by van den Berg et al. (2014) and Reeuwijk et al. (2014), it should be noted that the COC have previously expressed concern that the underlying approach of the ILSI/HESI framework described by Felter et al. (2011) was directed towards the US quantitative cancer risk assessment approach, which is not supported by the COC. However, the two papers instead use a MOE approach that is recommended by the COC.

40. Acrylamide (AA), through its metabolite glycidamide, is a genotoxic carcinogen that is found in certain food products, including those relevant to infants. EFSA evaluated the risk due to the presence of acrylamide in foods using a staged MOE approach (EFSA, 2015). The lowest $BMDL_{10}$ from data on incidences of Harderian gland adenomas and adenocarcinomas in male B6C3F1 mice were taken as a conservative endpoint for assessment of the risk for neoplastic effects of AA in humans. Age-specific exposures were derived from food consumption data for infants (<12 months), toddlers (≥ 1 year to < 3 years), other children (≥ 3 years to < 10 years), adolescents (≥ 10 years to < 18 years old), adults (≥ 18 years to < 65 years old, elderly (≥ 65 years to < 75 years old) and very elderly (≥ 75 years old).

41. EFSA calculated MOE values ranging from 425 (minimum lower bound, LB) to 89 (maximum upper bound, UB) for the mean exposure estimates, and from 283 (minimum LB) to 50 (maximum UB) for the 95th percentile exposure estimates across all surveys and age groups, as shown in Table 2. As the MOEs were all substantially lower than the guide value of 10,000, EFSA concluded that, although the available human studies have not demonstrated acrylamide to be a human carcinogen, the MOEs indicate a concern with respect to neoplastic effects (EFSA, 2015).

Table 2: Margins of exposure (MOE) values for neoplastic effects of AA across surveys and age groups.

Age Group	Mean		P95	
	Min LB	Max UB	Min LB	Max UB
Infants	340	106	121	68
Toddlers	189	89	121	50
Other children	189	106	121	53
Adolescents	425	189	189	85
Adults	425	283	213	131
Elderly	425	340	243	170
Very elderly	425	340	283	170

number of surveys used to derive the min/med/max mean exposure levels: 6; 10;17;16;16;13;11 per age group.
number of surveys used to derive the min/med/max 95th percentile exposure levels:5; 7; 17; 16; 16; 13; 9 per age group.

Summary

42. There does not appear to be one general approach applicable to all possible LTL exposures for adults and children, rather a set of principles to consider:

- The MOA will be crucial to an evaluation. If the MOA indicates that a chemical is directly DNA reactive, it is treated as a non-threshold carcinogen for which no level of exposure can be assumed to be without risk. Conversely, if the MOA indicates the chemical to be a threshold carcinogen, a triggering event may be identified (e.g. inflammation).

- The life stage at which exposures occur. This allows consideration of whether a specific exposure presents more, less, or even the same level of risk of a biological event occurring.

- Whether Haber's law may be used. Some limited uses may be helpful when used within known experimental durations. It is not applicable to low-dose extrapolation without a good knowledge of the MOA.

- Using an extra UF for children and infants should only be justified when supported by the scientific evidence. This may also apply to adults for shorter term exposure.

- The evidence that infants or children are more susceptible for most effects than adults is not currently supported, however data to allow such comparisons is limited.

Question for the Committee

i. How would Members propose to provide guidance on both the less than lifetime exposure and the margin of exposure for children? Can they be covered together, or should they be separate? Would Members propose that this forms part of the Guidance Statement series?

ii. Would a ‘guidance algorithm’ that asks a series of questions that should be addressed when considering LTL and/or MOE for infants and children be helpful? Although for many chemicals this might be a series of “don’t know” answers, such an algorithm would show that all aspects and uncertainties have been considered.

iii. Could parts of the US EPA approach be adopted, but based on the MOE approach instead of a quantitative risk approach.

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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Less than lifetime exposure to carcinogens – to incorporate margin of exposure for children

Details of Literature search carried out by NCET at WRc/IEH-C

Literature searches were performed by NCET at WRc/IEH-C under contract to PHE on 01/09/17 (unlimited date range) using the following search terms in PubMed, Scopus and Web of Science.

"less than lifetime" OR "less than lifetime exposure" OR "intermittent exposure" OR "fluctuating exposure" AND “risk assessment”

Total no. of papers retrieved (for screening) = 36

"less than lifetime" OR "less than lifetime exposure" OR "intermittent exposure" OR "fluctuating exposure" AND "child*"

Total number of papers retrieved (for screening) = 31

Additional searches were carried out on an ‘ad-hoc’ basis as needed through references cited in identified literature.