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ABSTRACT

Background: Conducting a risk assessment can be challenging, especially when dealing with several reference indices, which could lead to conflicting conclusions between studies. The common approach is to use a reference index from a single source based on the risk assessor's preference.

Objectives: To propose an approach for constructing a multi-reference index-based aggregated risk estimate using mathematical objectivity to reflect all of the available information.

Methods: The aggregated risk estimate based on multiple reference indices (AREMRI) results from the weighted linear combination of risk distributions that were obtained with each reference index available. The weights were calculated using the degree of agreement among the reference index-based risk distributions. The approach is illustrated through three practical cases of benzene inhalation cancer risk assessment using inhalation unit risks (IURs) from six different regulatory agencies.

Results: The degrees of agreement between the reference index-based risk distribution, obtained with the six IURs, ranged from 0.7 to 92%. The highest weights were attributed to reference index-based risk distributions that had the highest degree of agreement with the maximum number of other reference index-based risk distributions. Regardless of the practical case considered, the AREMRI risk distribution resulted in the third highest risk compared to the six single risk distributions.

Conclusion: Our approach can be useful in the presence of several reference indices by providing useful insights, consistency and direct comparisons between studies to support better-informed risk assessment and management decisions. This approach can shed some light on some of the uncertainties associated with the toxicological reference values in a risk assessment associated with the toxicological reference values. If the uncertainty is large, more detailed evaluation of the toxicological reference values would be needed.

KEYWORDS

Health risk assessment; probabilistic risk assessment; risk aggregation; cancer risk

1. Introduction

Risk assessments are paramount in ensuring the protection of human health against environmental pollutants (Rotter et al. 2018). Performing a risk assessment requires the use of toxicity reference indices. Reference indices are derived using rigorous methodological weights of evidence approaches by regulatory agencies based on available data generated in experimental toxicology and exposure assessment. For a given absorption pathway (oral, respiratory, cutaneous), dates when the index values were derived, the method of derivation, and knowledge or assumptions about substances' mechanisms of action are often different from one organization/agency/study to another (Petit et al. 2020). These differences arise mainly from the use of different data sources/key studies (e.g., the results from animal studies or epidemiological studies), extrapolation methods, correction factors, and commonly accepted assumptions and uncertainties (ANSES 2015; Beck et al. 2016; Melnick et al. 2008; US EPA 2014). Even when similar studies are considered for the same critical health effects and absorption pathway, organizations/agencies/studies can reach different conclusions due to different policies and/or expert judgments (Beck et al. 2016). Depending on the reference index chosen, the results of the risk assessment can thus differ and lead to different conclusions and decisions, which may have broad and profound implications regarding the prevention of adverse effects and the protection of human health and the environment.

The double question that arises when carrying out a risk assessment is knowing which reference index to use and how to take into account the information provided by the other indices. Indeed, there are no criteria or benchmark/gold standard approaches guiding the choice of an index, especially since, by definition, all reference indices available from health/regulatory agencies are legitimate. In practice, we tend to use either an index from our own home country agency (when available) or an index from an agency to which we subjectively attach a certain importance. Thus, in this paper, we explored and suggest an alternative approach, which would be to construct and use an aggregated risk estimate based on multiple reference indices (AREMRI) created from mathematical objectivity. Such an AREMRI would allow for direct comparisons among studies, promote transparency and ensure a consistency of analysis during risk assessment. The aim here is not to judge how researchers and/or

regulatory agencies derive reference indices or to criticize existing reference indices but rather to use them as is, starting from the fact that each of the indices carries a part of the truth.

The remainder of this paper is organized as follows. The general approach for constructing an AREMRI risk distribution (uncertain risks) is presented in Section 2. Section 3 is devoted to an illustrative application of the developed approach to inhalation cancer risks. Finally, the last section, Section 4, discusses the proposed approach and considers the practical implications and implementation of the developed analysis in an interactive web application.

2. Methods

2.1 Aggregated risk distribution construction based on multiple reference indices (AREMRI)

Consider a discrete ensemble of n indicators of uncertain risk r, each based on a reference index from a different source (e.g., organization/agency/study), and each being described by a distribution function normalized to one, $R_i(r)$, with $i = 1, 2, \dots, n$. It is assumed that all reference indices from n sources are legitimate and relevant (developed for the same purpose) and that there is no objective and/or impartial reason to choose one over another for the risk assessment. As a first step, the ensemble of n indicators can be characterized by the matrix of degrees of agreement, $\boldsymbol{A}$, given by (Eq. 1):

$$\boldsymbol{A} = \begin{pmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ a_{n1} & a_{n2} & \cdots & a_{nn} \end{pmatrix} = \begin{pmatrix} 1 & a_{12} & \cdots & a_{1n} \\ a_{21} & 1 & \cdots & a_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ a_{n1} & a_{n2} & \cdots & 1 \end{pmatrix} \quad (1)$$

where $a_{ij} = a_{ji}$ is the degree of agreement between two reference index-based distributions (indicators) i and j such that $0 \leq a_{ij} = a_{ji} \leq 1$ and $a_{ii} = 1$. $a_{ij} = 0$ refers to no agreement, while $a_{ij} = 1$ indicates total agreement between the two reference index-based risk distributions. A reference index-based distribution is defined as a risk distribution resulting from the use of a given/source-specific reference index (e.g., oral slope factor from US EPA). Mathematically, $a_{ij} = \text{overlap}[R_i, R_j]$ is obtained by calculating the overlap between two (normalized to one) distribution

functions $R_i(r)$ and $R_j(r)$; a general method for calculating the overlap (or overlapping area) between two functions is described elsewhere (Petit et al. 2020).

The content of $\boldsymbol{A}$ is very informative to compare reference index-based risk distribution with each other and also to guide the development of a pragmatic choice of one reference index over the others, in possible combination with other techniques such as stochastic dominance or expected utility (Verteramo Chiu et al. 2020). Whichever approach is used, the result would be to choose the indicator (i.e., reference index) from a single source (e.g., regulatory agency/study). Consequently, we are rather in favor of constructing a composite indicator resulting from the aggregation of all indicators to reflect all of the available information. Our aim is to develop such an aggregation based on the content of $\boldsymbol{A}$ and, in this case, there will be no aggregation when $\boldsymbol{A} = \mathbf{1}$ (identity matrix), i.e., when none of the reference index-based distributions would agree with the others.

To this end, we propose to construct an aggregated risk distribution based on multiple reference indices (AREMRI), $R_a(r)$, as a weighted linear combination of reference index-based risk distributions $R_i(r)$, as follows (Eq. 2):

$$R_a(r) = \sum_{i=1}^{n} \omega_i R_i(r) \tag{2}$$

where ω_i ($0 \leq \omega_i \leq 1$ such that $\sum_{i=1}^{n} \omega_i = 1$) is a contributing weight of the risk distribution generated with the reference index "i" and $R_i(r)$ is a risk distribution based on a single given reference index. Next, to determine the ω_i coefficients and obtain an objective aggregated distribution, we require that $R_a(r)$ has a maximum agreement with all risk distributions generated with all reference indices available $R_i(r)$, i.e., to maximize total agreement θ between $R_a(r)$ and all $R_i(r)$. The total agreement θ is related to the agreement matrix $\boldsymbol{A}$ as (Eq. 3):

$$\theta = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix}^{T} \underbrace{\begin{pmatrix} 1 & a_{12} & \cdots & a_{1n} \\ a_{21} & 1 & \cdots & a_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ a_{n1} & a_{n2} & \cdots & 1 \end{pmatrix}}_{\mathbf{A}} \begin{pmatrix} \omega_1 \\ \omega_2 \\ \vdots \\ \omega_n \end{pmatrix} \tag{3}$$

The agreement matrix $\mathbf{A}$ is symmetric with the trace, $\mathrm{Tr}(\mathbf{A}) = \sum_{k=1}^{n} \lambda_k = n$, where λ_k are the eigenvalues associated with (normalized to one) eigenvectors $\boldsymbol{v}_k$ of matrix $\mathbf{A}$ such that $0 \leq \lambda_1 < \lambda_2 <$

$\cdots < \lambda_n \leq n$. When there is no agreement among all reference index-based risk distributions $R_i(r)$, **A** reduces to the identity matrix with $a_{ij} = 0$ for $i \neq j$, and the total agreement is always $\theta = 1$ regardless of the weights ω_i. In this case, no aggregation based on the agreement matrix **A** is possible as there is no objective way of choosing one reference index over another. In the opposite situation when all $a_{ij} = 1$, i.e., perfect agreement among all reference index-based risk distributions, the total agreement is maximum, $\theta = n$. We will show below that, in this case, $\omega_i = 1/n$ (arithmetic mean). Finally, when $0 < a_{ij} < 1$, the maximum of the total agreement, θ, is obtained by setting the ω_i coefficients equal to eigenvector $\boldsymbol{v}_n$ corresponding to the largest eigenvalue λ_n as shown in (Eq. 4):

$$\begin{pmatrix}\omega_1\\ \omega_2\\ \vdots\\ \omega_n\end{pmatrix} = \frac{1}{\left[\sum_{i=1}^{n} v_{n,i}\right]}\begin{pmatrix}v_{n,1}\\ v_{n,2}\\ \vdots\\ v_{n,n}\end{pmatrix} \Longrightarrow \theta = \lambda_n \frac{1}{\left[\sum_{i=1}^{n} v_{n,i}\right]}\begin{pmatrix}1\\ 1\\ \vdots\\ 1\end{pmatrix}^{T}\begin{pmatrix}v_{n,1}\\ v_{n,2}\\ \vdots\\ v_{n,n}\end{pmatrix} = \lambda_n \qquad (4)$$

This determines the weights of $R_a(r)$ in Eq. 2. It is paramount to ensure that all $v_{n,i}$ have the same sign. Fig. 1 presents a schematic summary of the different steps of the construction of the aggregated risk distribution based on multiple reference indices.

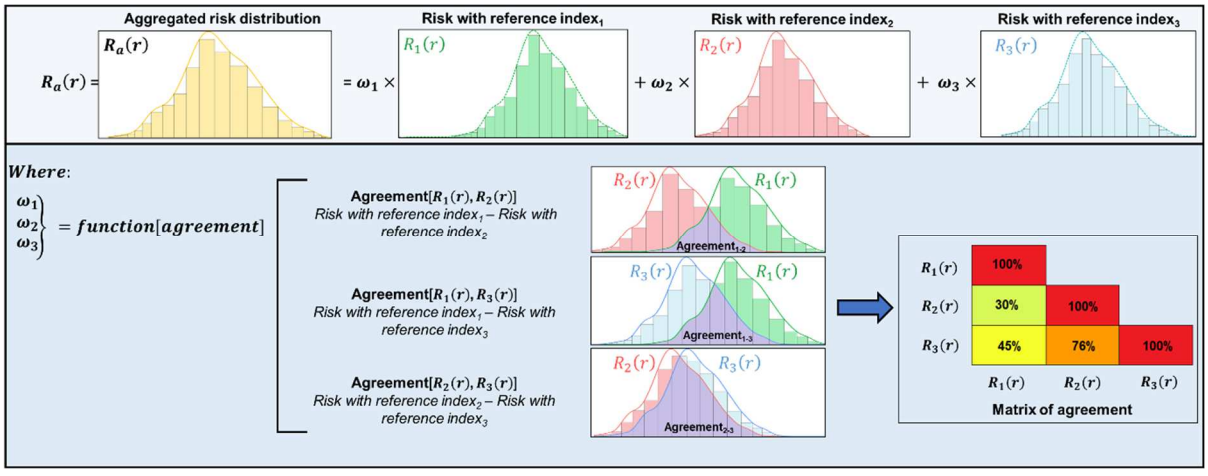


Fig. 1: Scheme of the general approach to construct an aggregated risk distribution based on multiple reference indices

ω_i: contributing weight of agency "i" with $0 \leq \omega_i \leq 1$ such that $\sum_{i=1}^{n} \omega_i = 1$; $R_a(r)$: aggregated risk distribution function based on multiple reference indices; $R_i(r)$: risk distribution function generated with reference index "i".

In case of perfect agreement among all reference index-based risk distributions (indicators), i.e., all $a_{ij} = 1$, the highest eigenvalue of the agreement matrix $\mathbf{A}$ is $\lambda_n = n$, associated with the eigenvector $\boldsymbol{v}_n{}^T = (1, 1, \cdots, 1)^T$; this leads to $\omega_1 = \omega_2 = \cdots = \omega_n = 1/n$.

When dealing with only two reference indices (indicators), i.e., $n = 2$ and $a_{12} = a_{21} \neq 0$, the highest eigenvalue of $\mathbf{A}$ is $\lambda_2 = 1 + a_{12}$, associated with the eigenvector $\boldsymbol{v}_2{}^T = (1, 1)^T$. In this case, the weights are $\omega_1 = \omega_2 = 1/2$, independent of a_{12}, provided that $a_{12} \neq 0$.

To gain more understanding of these weights, consider an example of $n = 3$ for which weights can be calculated explicitly as:

$$\boldsymbol{A} = \begin{pmatrix} 1 & a_{12} & 0 \\ a_{21} & 1 & a_{23} \\ 0 & a_{32} & 1 \end{pmatrix} \Longrightarrow \begin{pmatrix} \omega_1 \\ \omega_2 \\ \omega_3 \end{pmatrix} = \frac{1}{\left[a_{12} + \sqrt{a_{12}{}^2 + a_{23}{}^2} + a_{23}\right]} \begin{pmatrix} a_{12} \\ \sqrt{a_{12}{}^2 + a_{23}{}^2} \\ a_{23} \end{pmatrix} \quad (5)$$

where $a_{12} = a_{21} < 1$ and $a_{23} = a_{32} < 1$ such that $a_{13} = a_{31} = 0$, and the highest eigenvalue of $\mathbf{A}$ is $\lambda_3 = 1 + \sqrt{a_{12}{}^2 + a_{23}{}^2}$. Clearly, Eq. 5 shows how the weights are "proportional or a function" of the respective agreements. For instance, setting $a_{23} = 0$ leads to $\omega_3 = 0$, i.e., the contribution of a reference index-based risk distribution (indicator) is zero when the reference index-based risk distribution does not agree with any other. In addition, the weight of a reference index-based risk distribution (indicator) increases with its total agreement with the other reference index-based risk distributions (indicators). Indeed, we have $\omega_3 < \omega_1 < \omega_2$ when $a_{23} < a_{12}$, and $\omega_1 < \omega_3 < \omega_2$ for $a_{23} > a_{12}$. These observations remain valid for $n > 3$.

2.2 Application to inhalation cancer risks

To illustrate the usefulness of using an aggregated risk distribution based on multiple reference indices, we consider three practical cases/scenarios of risk assessment of benzene exposure where each exposure scenario is characterized by a distribution of benzene concentrations assumed constant over time and following a lognormal distribution with the geometric mean (GM) and geometric standard deviation (GSD) parameters given in Table 1 and an exposure duration of 4 hours a day, 120 days a

154 year for 50 years. Regardless of the reference index considered, the concentration distributions used
155 for a given scenario were exactly the same (same geometric mean and geometric standard deviation).
156 The concentration distribution parameters differed from one practical case to another with a GM set to
157 253, 253 and 58.4 µg/m^3 and a GSD set to 2.80, 1.03 and 2.80 for cases 1, 2 and 3, respectively. For
158 all scenarios, both the GM and GSD were set at pragmatic random values generated with R software
159 4.0.5® (R Core Team, Vienna, Austria) for Windows 10©.
160 We used the *InCaRisk* app (Petit et al. 2020) with 1,000 simulations runs to generate all of the
161 reference index-based risk distributions $R_i(r)$. Briefly, the *InCaRisk* app is a free user-friendly and
162 interactive web application that allows for cancer risk estimation following inhalation exposure
163 (https://exporisk-timc.imag.fr/InCaRisk/). A total of 305 substances/chemicals with reference values
164 from up to eight agencies are available. *InCaRisk* requires no programming knowledge to use. This
165 app also incorporates a variety of features and options to make it easy to use, with the possibility of
166 configuring the exposure settings (exposure scenario), the concentration distribution settings (choice
167 of the type of distribution, distribution parameters, uploading an exposure concentration file) and to
168 export the results as a report. This app offers the chance to have an immediate glimpse into the results
169 and to see how the results change according to different setting configurations with interactive easy-to-
170 read graphs, which are downloadable.
171 The reference index-based risk distributions $R_i(r)$ were generated for six sanitary agencies for which
172 the tumor site (leukemia) and tumor type (hematologic/immune) used in the inhalation unit risk (IUR)
173 establishment were the same: ANSES (French Agency for Food, Environmental and Occupational
174 Health & Safety), Health Canada, OEHHA (California Office of Environmental Health Hazard
175 Assessment), RIVM (National Dutch Institute for Public Health and the Environment), US EPA (US
176 Environmental Protection Agency) and WHO (World Health Organization). The IURs for benzene set
177 by these agencies regarding the risk of leukemia for lifetime exposure were 2.6x10^{-5} (ANSES 2019),
178 3.3x10^{-6} (Health Canada 2010), 2.9x10^{-5} (OEHHA 2019), 5x10^{-6} (RIVM 2001), 7.8x10^{-6} (US EPA
179 2018) and 6x10^{-6} m^3/µg (WHO 2000).
180
181 Table 1 here (see Table 1 after the Reference section).

3. Results

For a given practical case, each IUR-based risk distribution resulted in different cancer estimates even though the exposure concentration distributions were the same. These differences came solely from the IUR values that differed from one agency to another (Table 1). Indeed, each IUR-based risk distribution had the same shape (height and width) because of similar concentration parameters (Table 1) but was shifted from one another (different mean) by a factor that depended on the ratio $IUR_{agency\ i}/IUR_{agency\ j}$ (Fig. 2C, 3C and 4C).

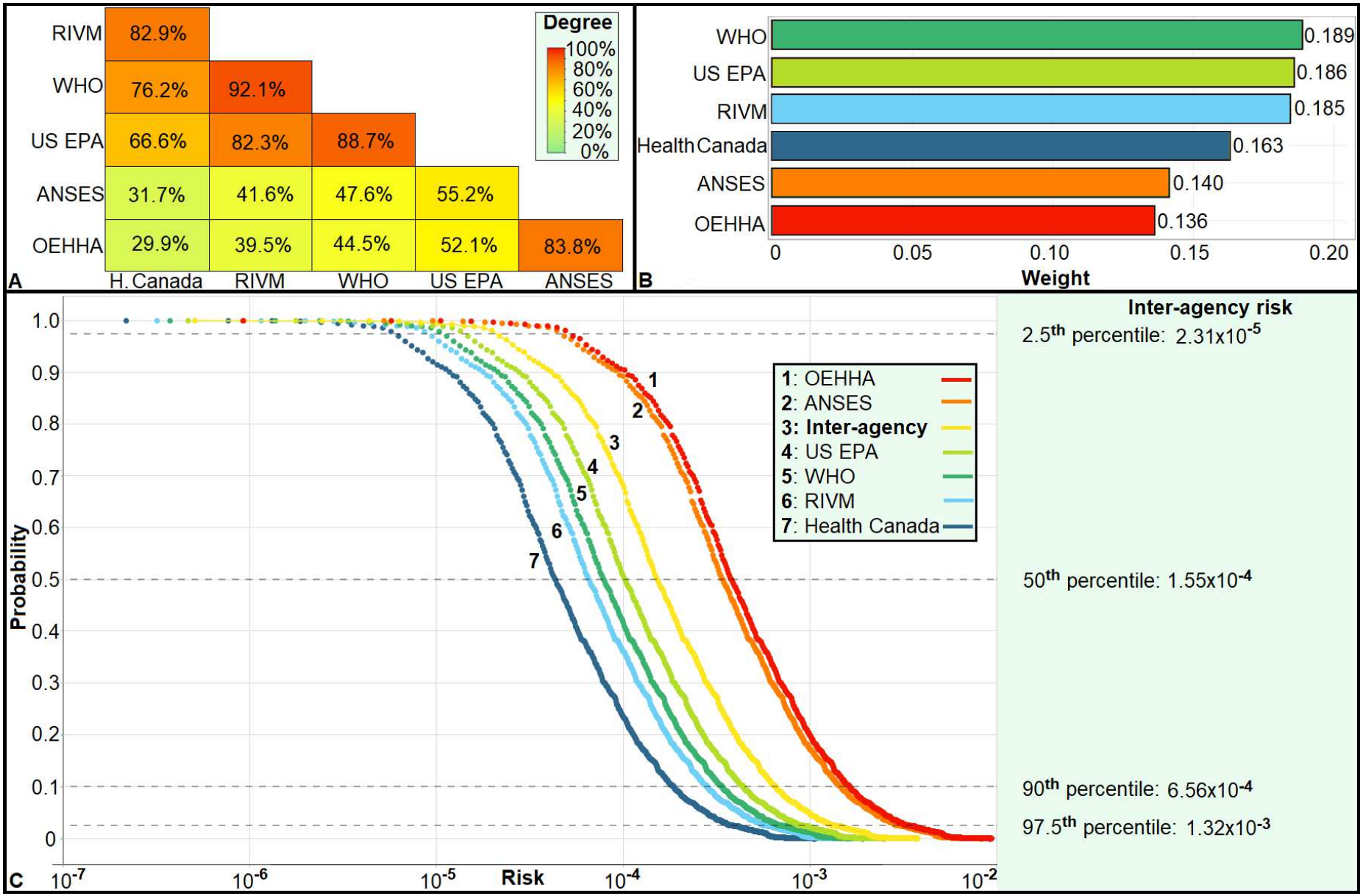
As seen in the matrix of agreement between sources (agencies) (Fig. 2A, 3A and 4A), the degrees of agreement were heterogeneous between IUR-based risk distributions, regardless of the practical case considered. The results were similar for cases 1 and 3. Degrees of agreement were lower for the second scenario than for the first and third scenarios because the GSDs were the lowest (narrower distributions) for case 2. For all scenarios, the highest degrees of agreement, 92% for cases 1 and 3 and 81% for case 2, were found between IUR-based risk distributions from RIVM and WHO, while the lowest degrees of agreement were found between IUR-based risk distributions from Health Canada and OEHHA (30% for cases 1 and 3, 0.7% for case 2). Regardless of the practical case considered, IUR-based risk distributions from OEHHA and ANSES had a high degree of agreement with each other (84% for cases 1 & 3, 80% for case 2), a medium degree of agreement with all other IUR-based risk distributions for cases 1 & 3 (30 to 56%), and a low degree of agreement with all other IUR-based risk distributions for case 2 (0.7 to 15%). IUR-based risk distributions from the WHO, US EPA, Health Canada and RIVM had a medium to high degree of agreement with each other (66 to 92% for cases 1 & 3 and 30 to 81% for case 2).

The weights were similar for cases 1 and 3, ranging from 0.136 to 0.189, and they ranged from 0.053 to 0.247 for case 2 (Fig. 2B, 3B and 4B). The highest weights were attributed to IUR-based risk distributions that had the highest degree of agreement with the maximum number of other IUR-based risk distributions. Conversely, IUR-based risk distributions that shared a high degree of agreement with the smallest number of other IUR-based risk distributions had the smallest weights.

For the first and third scenarios, the aggregated multi IUR-based risk distribution (AREMRI) followed a lognormal distribution of parameters GM = $1.65x10^{-4}$ and GSD = 2.8 for case 1 and GM = $3.82x10^{-5}$ and GSD = 2.84 for case 3. The AREMRI resulted in the third highest risk, with a leukemia risk of $6.56x10^{-4}$ [IC 95%: $2.31x10^{-5}$ – $1.32x10^{-3}$] for case 1 and $1.53x10^{-4}$ [IC 95%: $5.30x10^{-6}$ – $3.07x10^{-4}$] for case 3. For both scenarios, these leukemia risks were 2.5 and 2.2 times lower than the cancer risk estimated with the reference indices (IURs) of OEHHA and ANSES, respectively (Fig. 2C and 4C). Conversely, the aggregated multi-IUR-based risks were 1.5, 1.9, 2.3 and 3.5 times higher than the leukemia risk estimated with the reference indices from the US EPA, WHO, RIVM and Health Canada, respectively. The concentration GSDs used for cases 1 & 3 were the same (GSD = 2.80), which explains why the weights and degrees of agreement were similar for both scenarios. The only difference between case 1 and case 3 came from the estimated leukemia risk, which was 4.3 times lower for case 3 than for case 1. This difference corresponded to the ratio of their concentration GM (253 µg/m^3 for case 1 *vs.* 58.4 µg/m^3 for case 3). In other words, for a given concentration GSD, changing the concentration GM will shift the risk estimate toward higher values when the GM is increased and toward lower values when the GM is decreased, with little to no change at all of the degrees of agreement or the weighted values.

For the second scenario, the aggregated multi-IUR-based risk distribution (AREMRI) followed a lognormal distribution of parameters GM = $1.08x10^{-4}$ and GSD = 1.52. The AREMRI resulted in the third highest risk, with a leukemia risk of $1.83x10^{-4}$ [IC 95%: $4.77x10^{-5}$ – $2.55x10^{-4}$], which was 3.5 and 3.1 times lower than the cancer risk estimated with the reference indices (IURs) of OEHHA and ANSES, respectively (Fig. 3C). Conversely, the aggregated multi-IUR-based risk was 1.1, 1.4, 1.6 and 2.5 times higher than the leukemia risk estimated with the reference indices from the US EPA, WHO, RIVM and Health Canada, respectively. For this scenario, the GM concentration was the same as that in the first scenario (GM = 253 µg/m^3), but the GSD concentration was lower (1.03 for case 2 *vs.* 2.80 for case 1). A lower GSD concentration for case 2 resulted in lower degrees of agreement (Fig. 3A) and better risk estimation (narrower 95% confidence interval) than for case 1. Indeed, there was a 5.3

237 factor between the lower and upper bounds of the 95% confidence interval of the risk distribution for
238 case 2 compared to a factor of 57 for case 1.


RIVM
WHO
US EPA
ANSES
OEHHA
82.9%
76.2%
92.1%
66.6%
82.3%
88.7%
31.7%
41.6%
47.6%
55.2%
29.9%
39.5%
44.5%
52.1%
83.8%
H. Canada
RIVM
WHO
US EPA
ANSES
Degree
100%
80%
60%
40%
20%
0%
A
WHO
US EPA
RIVM
Health Canada
ANSES
OEHHA
0.189
0.186
0.185
0.163
0.140
0.136
0
0.05
0.10
0.15
0.20
Weight
B
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
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0
1
2
3
4
5
6
7
1: OEHHA
2: ANSES
3: Inter-agency
4: US EPA
5: WHO
6: RIVM
7: Health Canada
10^{-7}
10^{-6}
10^{-5}
Risk
10^{-4}
10^{-3}
10^{-2}
C
Inter-agency risk
2.5th percentile: 2.31×10^{-5}
50th percentile: 1.55×10^{-4}
90th percentile: 6.56×10^{-4}
97.5th percentile: 1.32×10^{-3}

239

240 **Fig. 2**: Side-by-side comparison of single IUR-based risk distributions for the construction of the aggregated multi-IUR-based risk distribution – case 1

241 A: Matrix of degrees of agreement between a single IUR-based risk distribution, B: Weights attributed to the IUR-based risk distribution for the aggregated

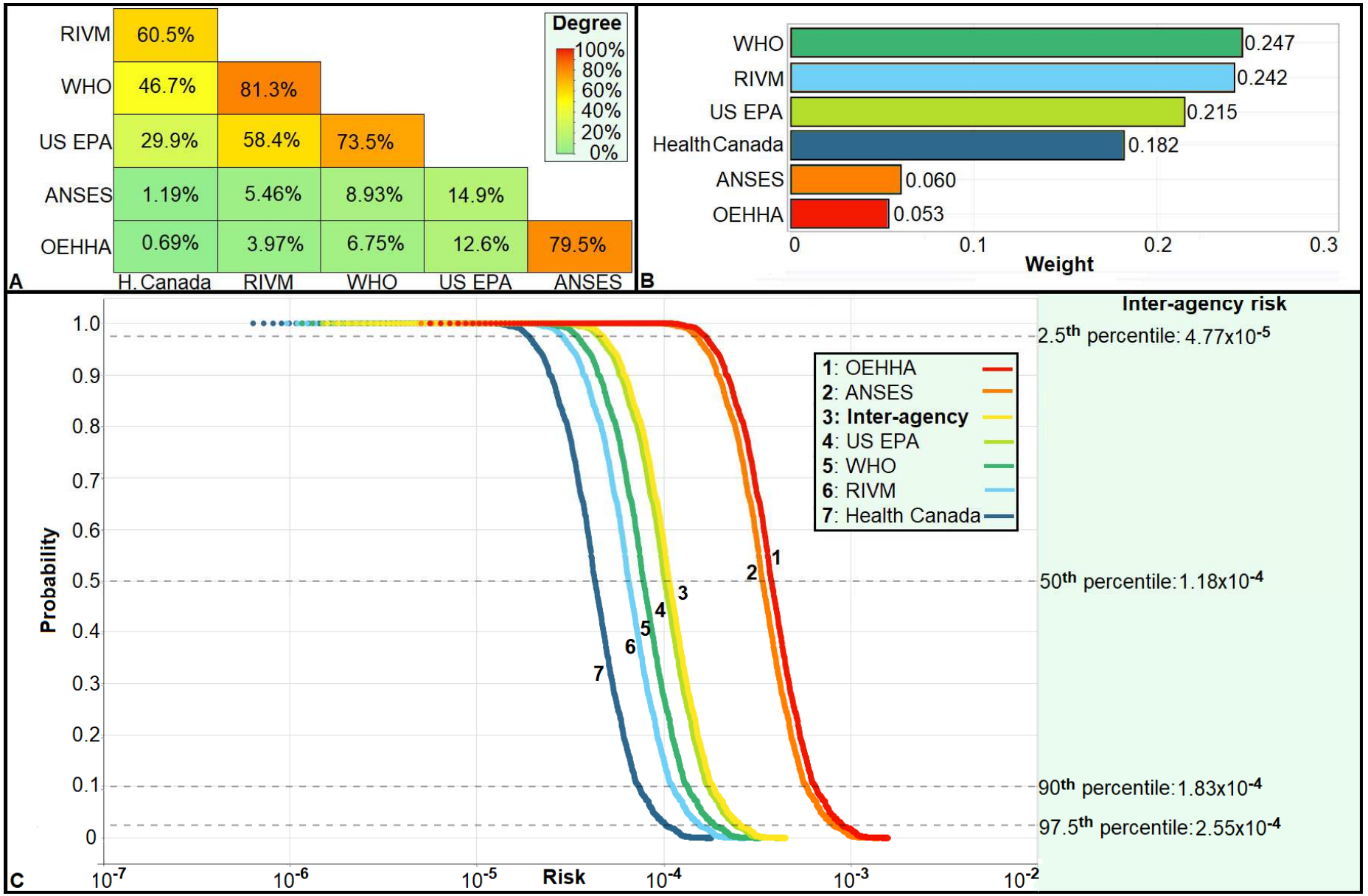
242 multi-IUR-based risk distribution construction, C: IUR-based risk distributions.

243 ANSES: French Agency for Food, Environmental and Occupational Health & Safety, H. Canada: Health Canada, OEHHA: California Office of

244 Environmental Health Hazard Assessment, RIVM: National Dutch Institute for Public Health and the Environment, US EPA: US Environmental Protection

245 Agency, WHO: World Health Organization. Each agency name refers to the risk distribution generated using its benzene IUR and the exposure scenario

246 considered. The term "Inter-agency" refers here to the aggregated risk estimate based on multiple reference indices (AREMRI).


A
RIVM
WHO
US EPA
ANSES
OEHHA
60.5%
46.7%
81.3%
29.9%
58.4%
73.5%
1.19%
5.46%
8.93%
14.9%
0.69%
3.97%
6.75%
12.6%
79.5%
H. Canada
RIVM
WHO
US EPA
ANSES
Degree
100%
80%
60%
40%
20%
0%
B
WHO
RIVM
US EPA
Health Canada
ANSES
OEHHA
0.247
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0.215
0.182
0.060
0.053
0
0.1
0.2
0.3
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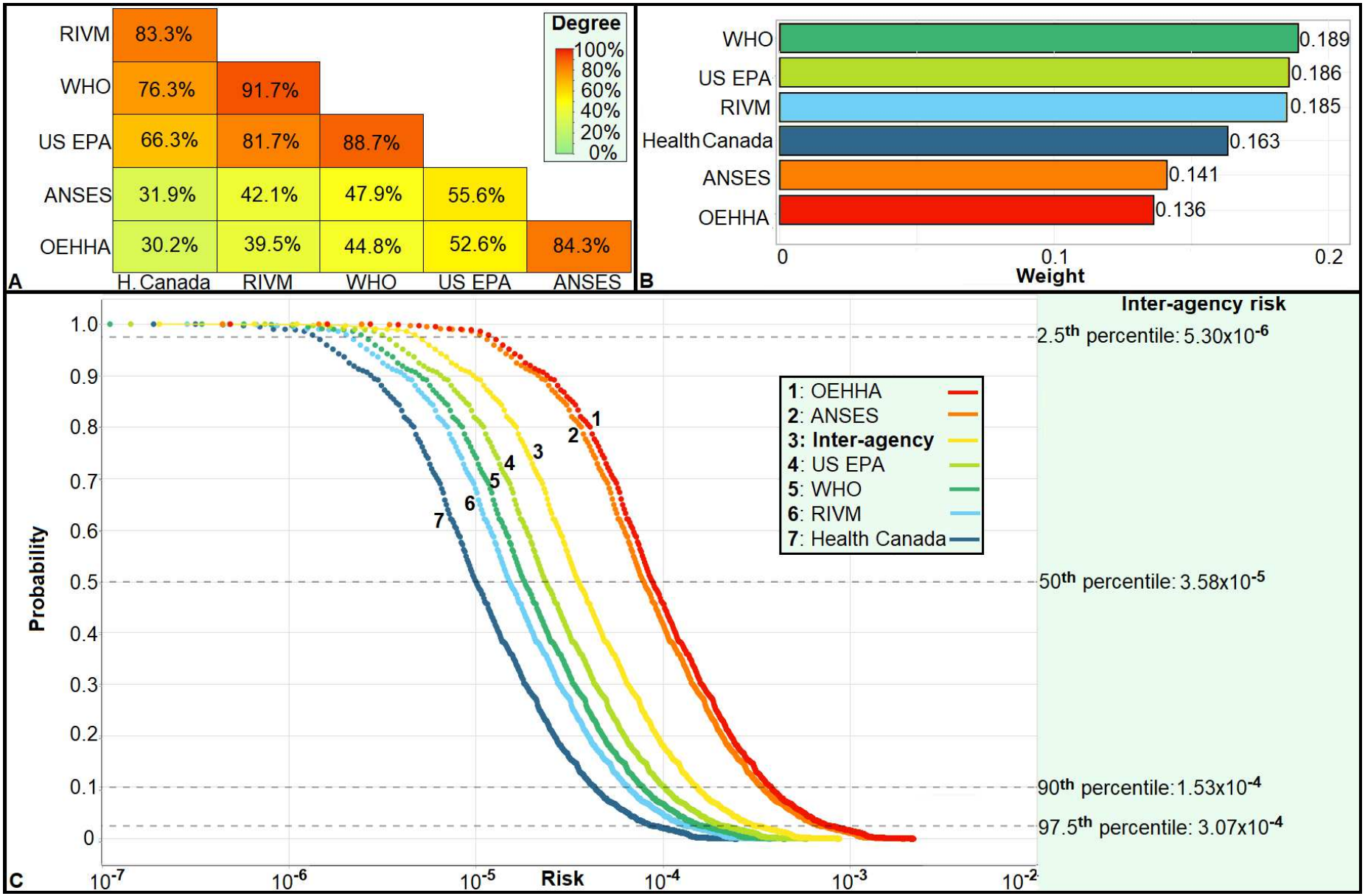
C
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10^{-7}
10^{-6}
10^{-5}
Risk
10^{-4}
10^{-3}
10^{-2}
1: OEHHA
2: ANSES
3: Inter-agency
4: US EPA
5: WHO
6: RIVM
7: Health Canada
Inter-agency risk
2.5th percentile: 4.77x10-5
50th percentile: 1.18x10-4
90th percentile: 1.83x10-4
97.5th percentile: 2.55x10-4

247

Fig. 3: Side-by-side comparison of single IUR-based risk distributions for the construction of the aggregated multi-IUR-based risk distribution – case 2

A: Matrix of degrees of agreement between a single IUR-based risk distribution, B: Weights attributed to the IUR-based risk distribution for the aggregated multi-IUR-based risk distribution construction, C: IUR-based risk distributions.

ANSES: French Agency for Food, Environmental and Occupational Health & Safety, H. Canada: Health Canada, OEHHA: California Office of Environmental Health Hazard Assessment, RIVM: National Dutch Institute for Public Health and the Environment, US EPA: US Environmental Protection Agency, WHO: World Health Organization. Each agency name refers to the risk distribution generated using its benzene IUR and the exposure scenario considered. The term "Inter-agency" refers here to the aggregated risk estimate based on multiple reference indices (AREMRI).


A
RIVM
WHO
US EPA
ANSES
OEHHA
83.3%
76.3%
91.7%
66.3%
81.7%
88.7%
31.9%
42.1%
47.9%
55.6%
30.2%
39.5%
44.8%
52.6%
84.3%
H. Canada
RIVM
WHO
US EPA
ANSES
Degree
100%
80%
60%
40%
20%
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B
WHO
US EPA
RIVM
Health Canada
ANSES
OEHHA
0.189
0.186
0.185
0.163
0.141
0.136
0
0.1
0.2
Weight
C
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10^{-7}
10^{-6}
10^{-5}
10^{-4}
10^{-3}
10^{-2}
Risk
1
2
3
4
5
6
7
1: OEHHA
2: ANSES
3: Inter-agency
4: US EPA
5: WHO
6: RIVM
7: Health Canada
Inter-agency risk
2.5th percentile: 5.30x10-6
50th percentile: 3.58x10-5
90th percentile: 1.53x10-4
97.5th percentile: 3.07x10-4

255

Fig. 4: Side-by-side comparison of single IUR-based risk distributions for the construction of the aggregated multi-IUR-based risk distribution – case 3

A: Matrix of degrees of agreement between a single IUR-based risk distribution, B: Weights attributed to the IUR-based risk distribution for the aggregated multi-IUR-based risk distribution construction, C: IUR-based risk distributions.

ANSES: French Agency for Food, Environmental and Occupational Health & Safety, H. Canada: Health Canada, OEHHA: California Office of Environmental Health Hazard Assessment, RIVM: National Dutch Institute for Public Health and the Environment, US EPA: US Environmental Protection Agency, WHO: World Health Organization. Each agency name refers to the risk distribution generated using its benzene IUR and the exposure scenario considered. The term "Inter-agency" refers here to the aggregated risk estimate based on multiple reference indices (AREMRI).

4. Discussion

Performing a risk assessment requires the use of toxicity reference indices. When dealing with several reference indices, risk assessment can be challenging, as there is no objective way to choose one reference index over the others. By definition, all indices available from sanitary/regulatory agencies are legitimate, but in practice, we tend to use an index from a source or agency to which we subjectively attach a certain importance. In this paper, we propose a novel approach consisting of constructing and using an aggregated multi-reference index-based risk estimate constructed only on mathematical objectivity, assuming that the reference indices considered are all relevant and suitable for the risk assessment to be conducted. An R code allowing for the estimation of risks (AREMRI) by inputting multiple reference indices is provided in the Supplemental Material.

The construction of the aggregated risk distribution was based on the weighted linear aggregation (arithmetic mean) of the probability risk distribution generated using a given reference index and using the degree of agreement among the reference index-based risk distributions for the assignment of weight. Other approaches could be used, such as stochastic dominance, which is a form of stochastic ordering that would favor one reference index-based risk distribution over the others based on a specific criterion. For example, using stochastic dominance, it would be possible to favor only the risk distribution resulting from the source or agency with the highest reference index, that is to say the most protective, or with the lowest reference index (weight of 1 while a weight of 0 for all the other reference index-based risk distribution) (Verteramo Chiu et al. 2020). That kind of approach is, however, different from our goal, which was not to judge or provide arguments for choosing a reference index over the others but rather to objectively construct an aggregated risk indicator that takes into account several reference indices from different sources (e.g., sanitary agencies), as all reference indices are legitimate and carry part of the truth.

The proposed approach was illustrated using three practical cases where the exposure concentration distributions were assumed to follow lognormal distributions. Our approach is not limited to lognormal distributions and can work with any type of distribution. Two additional examples are available in the Supplemental Material (Fig. S1 and S2), with exposure concentrations following normal and Poisson distributions, respectively.

The approach consisting of constructing and using an aggregated multi-reference index-based risk estimate was illustrated for one kind of stochastic reference value (inhalation cancer unit risk). The presented approach could be used with other types of toxicological reference values, such as oral slope factors, drinking water unit risks or threshold/deterministic values. For some toxicological reference values, the distribution of the underlying toxicity data is available, and the reference value itself can sometimes correspond to a certain point on that distribution (e.g., for BMDL values). In that particular case, these reference values could potentially be set as distributions instead of single values using the distribution of the underlying toxicity data when available. While the presented approach can still be used with reference value distributions, it should be noted that the choice of the reference value distribution (e.g., gamma, lognormal, Poisson, Weibull) and the associated uncertainties (confidence intervals) will both have an important impact on the resulting risk estimate. In particular, in the presence of large confidence intervals (high data dispersion), the degrees of agreement (overlaps between distributions of risks) are so high that all of the reference indices contribute almost equally to the aggregate distribution and the notion of multi-reference indices becomes less relevant. This issue is particularly true with deterministic values (threshold values), for which the choice of the derivation method and, in particular, the choice and use of large safety factors may dominate the differences between the toxicological reference values. One possible solution to address this issue would be to replace traditional noncancer reference doses (threshold values) with probabilistic estimates (Chiu et al. 2018).

Regardless of the practical case considered, IUR-based risk distributions from OEHHA and ANSES had a high degree of agreement with each other but a medium to low degree of agreement with other IUR-based risk distributions. The six benzene reference values used in this illustration were derived for the same purpose (lifetime benzene exposure), all based on cohort studies of benzene-exposed workers, but using different key studies and extrapolation/derivation methods among agencies, which may explain the observed differences (ANSES 2019; Health Canada 2010; OEHHA 2019; RIVM 2001; US EPA 2018; WHO 2000). OEHHA and ANSES used the same extrapolation method, a relatively risk procedure, but chose two different key studies, Rinsky et al. (1981) for OEHHA and Richardson (2008) for ANSES. RIVM chose the same key study as OEHHA but used a nonthreshold

319 extrapolation method. The WHO used an average relative risk model with Crump (1994) as a key
320 study. The US EPA applied a low-dose linearity utilizing the maximum likelihood estimates method
321 based on six key studies (Crump and Allen 1984; Crump 1994; Paustenbach et al. 1993; Rinsky et al.
322 1981, 1987; US EPA 1998). Health Canada applied a linear quadratic model of the exposure response
323 relationship based on four key studies (Bond et al. 1986; Rinsky et al. 1987; Wong 1987a,b).
324 Differences in policies and/or expert judgments could also have played a role in the observed
325 differences (Beck et al. 2016).
326 The aggregated multi-reference index-based distribution (the degrees of agreement and weights)
327 depends on the number of reference indices included in the aggregation as well as the concentration
328 distribution parameters. The narrower the concentration distributions (lower GSD), the lower the
329 degrees of agreement and the better the risk distribution estimation (narrower confidence interval). If
330 the GSD concentration tends to 1, as in the second scenario, the AREMRI tends to the mean risk value
331 and also tends to approach and equal a single reference index-based risk distribution (e.g., the risk
332 distribution using the reference value from the US EPA for case 2).
333 Regarding the reference indices, we found, for our practical cases, six agencies that set/proposed an
334 IUR for benzene and the risk of leukemia. There are most likely other agencies and studies around the
335 world which we are not aware of that may also have proposed an IUR for benzene and the risk of
336 leukemia for lifetime exposure. Integrating these potential other IURs into the aggregated multi-
337 reference index-based risk distribution construction would change the leukemia risk obtained with the
338 aggregated risk indicator. However, the approach presented in this paper does not remove the
339 requirement of a prior screening of reference values to be included in the integrated approach. This
340 screening should always be made to determine how reference indices were derived, which data they
341 are based on, and their intended use (e.g., assessment of occupational exposure, exposure via
342 foodstuffs and unintentional exposure). Indeed, it is paramount that the risk assessor has some
343 knowledge regarding the reference values used in an assessment and understands the way the values
344 were derived, their associated uncertainties and their relevance and validity for the risk assessment
345 being carried out. If the approach presented in this paper is used to interpret the results of a risk

assessment, then only reference values derived for the same purpose(s) should be included in the analysis.

5. Conclusions

The three practical cases highlighted the usefulness of comparing risk estimates generated using multiple reference indices from several sources (e.g., regulatory agencies) when assessing the human health risk associated with exposure to environmental pollutants.

Therefore, the proposed approach hinges on its ability to provide useful information when conducting risk assessment in the presence of several reference indices from various sources. These results are essential for risk managers, practitioners, and decision-makers by providing guidance and by supporting direct comparisons between studies. Indeed, our approach can provide a more complete, consistent and transparent risk assessment of pollutants that pose a threat to human health and support better-informed risk management decisions by giving some insight into the uncertainties associated with the choice of the reference index in the risk assessment. Our approach could also serve to integrate risk assessments, such as by obtaining an integrated view of risk assessments when trying to prioritize among different cases for remedial action.

To facilitate the use of our approach, the matrix of degrees of agreement, side-by-side comparison of reference index-based risk distributions, the choice of the reference values to consider and the construction of the aggregated multi-reference index-based risk distribution will be implemented in the *InCaRisk* app for inhalation cancer risk assessment. In addition to making information more readily understood and retained in a quicker time, the visual aids and representations provided by *InCaRisk* could be useful for improving risk communication and promoting transparency among studies when conducting risk assessments (Beck et al. 2016).

Regardless of the type of exposure (e.g., acute, subchronic, or chronic), absorption pathways, exposure setting (environmental or occupational), stages of the life cycle of a chemical (e.g., manufacture, use, disposal, consumer products or waste) and stages of the life of an individual (e.g., adulthood), the approach presented in this paper can be used. However, this approach can only be used with reference indices intended for the same purpose (e.g., the same absorption pathway, same type of exposure and

same exposure setting), and some prior screening of reference indices has to be done to ensure that the aggregated approach does not look at a mixture of reference values that should not be integrated. Finally, the proposed approach has applicability in other fields and studies with similar problematics, as long as there is some constraint on the choice of reference values to be included.

Author contributions

Pascal Petit: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualization. **Dominique J. Bicout**: Conceptualization, Methodology, Validation, Writing - Review & Editing.

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464 **Tables**

465

466 **Table 1**: Summary of the lognormal exposure concentration distribution parameters used for three
467 practical cases

Reference index source	Reference index	Case 1	Case 2	Case 3
	IUR ($m^3/\mu g$)	GM; GSD	GM; GSD	GM; GSD
Using the reference index from ANSES	$2.6x10^{-5}$	253 $\mu g/m^3$; 2.80	253 $\mu g/m^3$; 1.03	58.4 $\mu g/m^3$; 2.80
Using the reference index from Health Canada	$3.3x10^{-6}$	253 $\mu g/m^3$; 2.80	253 $\mu g/m^3$; 1.03	58.4 $\mu g/m^3$; 2.80
Using the reference index from OEHHA	$2.9x10^{-5}$	253 $\mu g/m^3$; 2.80	253 $\mu g/m^3$; 1.03	58.4 $\mu g/m^3$; 2.80
Using the reference index from RIVM	$5.0x10^{-6}$	253 $\mu g/m^3$; 2.80	253 $\mu g/m^3$; 1.03	58.4 $\mu g/m^3$; 2.80
Using the reference index from US EPA	$7.8x10^{-6}$	253 $\mu g/m^3$; 2.80	253 $\mu g/m^3$; 1.03	58.4 $\mu g/m^3$; 2.80
Using the reference index from WHO	$6.0x10^{-6}$	253 $\mu g/m^3$; 2.80	253 $\mu g/m^3$; 1.03	58.4 $\mu g/m^3$; 2.80

468 *Note*: GM: geometric mean; GSD: geometric standard deviation, IUR: inhalation unit risk, ANSES:
469 French Agency for Food, Environmental and Occupational Health & Safety, H. Canada: Health
470 Canada, OEHHA: California Office of Environmental Health Hazard Assessment, RIVM: National
471 Dutch Institute for Public Health and the Environment, US EPA: US Environmental Protection
472 Agency, WHO: World Health Organization.

Figure captions

Fig. 1: Scheme of the general approach to construct an aggregated risk distribution based on multiple reference indices

ω_i: contributing weight of agency "i" with $0 \leq \omega_i \leq 1$ such that $\sum_{i=1}^{n} \omega_i = 1$; $R_a(r)$: aggregated risk distribution function based on multiple reference indices; $R_i(r)$: risk distribution function of agency "i".

Fig. 2: Side-by-side comparison of single IUR-based risk distributions for the construction of the aggregated multi-IUR-based risk distribution – case 1

A: Matrix of degrees of agreement between a single IUR-based risk distribution, B: Weights attributed to the IUR-based risk distribution for the aggregated multi-IUR-based risk distribution construction, C: IUR-based risk distributions.

ANSES: French Agency for Food, Environmental and Occupational Health & Safety, H. Canada: Health Canada, OEHHA: California Office of Environmental Health Hazard Assessment, RIVM: National Dutch Institute for Public Health and the Environment, US EPA: US Environmental Protection Agency, WHO: World Health Organization. Each agency name refers to the risk distribution generated using its benzene IUR and the exposure scenario considered. The term "Inter-agency" refers here to the aggregated risk estimate based on multiple reference indices (AREMRI).

Fig. 3: Side-by-side comparison of single IUR-based risk distributions for the construction of the aggregated multi-IUR-based risk distribution – case 2

A: Matrix of degrees of agreement between a single IUR-based risk distribution, B: Weights attributed to the IUR-based risk distribution for the aggregated multi-IUR-based risk distribution construction, C: IUR-based risk distributions.

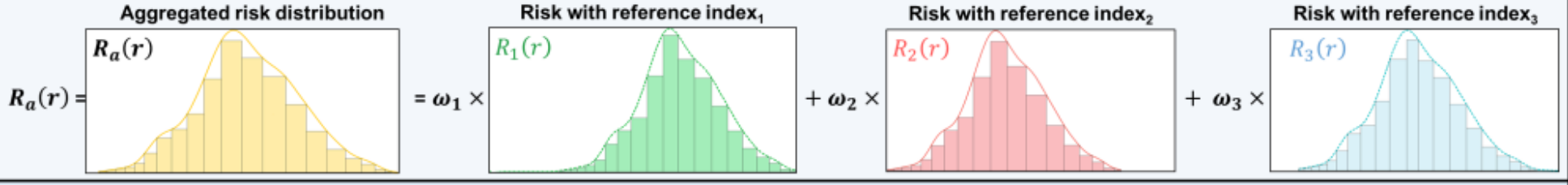
ANSES: French Agency for Food, Environmental and Occupational Health & Safety, H. Canada: Health Canada, OEHHA: California Office of Environmental Health Hazard Assessment, RIVM: National Dutch Institute for Public Health and the Environment, US EPA: US Environmental

Protection Agency, WHO: World Health Organization. Each agency name refers to the risk distribution generated using its benzene IUR and the exposure scenario considered. The term "Inter-agency" refers here to the aggregated risk estimate based on multiple reference indices (AREMRI).

Fig. 4: Side-by-side comparison of single IUR-based risk distributions for the construction of the aggregated multi-IUR-based risk distribution – case 3

A: Matrix of degrees of agreement between a single IUR-based risk distribution, B: Weights attributed to the IUR-based risk distribution for the aggregated multi-IUR-based risk distribution construction, C: IUR-based risk distributions.

ANSES: French Agency for Food, Environmental and Occupational Health & Safety, H. Canada: Health Canada, OEHHA: California Office of Environmental Health Hazard Assessment, RIVM: National Dutch Institute for Public Health and the Environment, US EPA: US Environmental Protection Agency, WHO: World Health Organization. Each agency name refers to the risk distribution generated using its benzene IUR and the exposure scenario considered. The term "Inter-agency" refers here to the aggregated risk estimate based on multiple reference indices (AREMRI).



Where:

$$\left.\begin{matrix}\omega_1\\ \omega_2\\ \omega_3\end{matrix}\right\} = function[agreement]$$

Agreement$[R_1(r), R_2(r)]$
Risk with reference index$_1$ – Risk with reference index$_2$

Agreement$[R_1(r), R_3(r)]$
Risk with reference index$_1$ – Risk with reference index$_3$

Agreement$[R_2(r), R_3(r)]$
Risk with reference index$_2$ – Risk with reference index$_3$