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Formulation and application of the probability of exceedance metric for risk characterization of non-threshold chemical hazards in food

Abstract

The aim of this work is to present the rationale, formulation, and application of the probability of exceedance (POE) as a metric capable of characterizing public health risks due to exposure to non-threshold chemical hazards in food. One of the main advantages of this metric is that it complements the information provided by the MOE and supports risk managers in decision-making, especially when the distribution of the estimated intake is positively biased. For a better understanding of its benefits, MOE and POE values were calculated in relation to the exposure to inorganic arsenic (iAs) and lead (Pb) in the diet of the Australian, Chinese, European, Japanese and American adult populations. The findings showed that similar MOE values, and therefore similar levels of concern, can have differences in POE results of up to several orders of magnitude, suggesting that more effective risk management measures should be prioritised.

Keywords

Chemical hazards, Arsenic, Lead, Diet, Margin of exposure, Risk characterization, Risk-informed decision-making.

1. Introduction

Metals, natural constituents of the environment, have increased their concentrations above their natural levels due to natural and human activities and now even contaminate our food (Kachenko & Singh, 2006; Perez, et al., 2018). Metals consumed in food accumulate in the body and may reach toxic levels, creating problems such as cardiovascular, kidney and bone diseases, which can lead to serious damage to health over time (Ferrante, et al., 2019; Signorelli, et al., 2019; Fiore et al., 2020). The control of consumers' exposure to metals in food has thus long been and continues to be a matter of food safety concern.

Risk assessment is now being used as a tool to support decision-making processes in food safety management policies to protect consumers' health. It consists of the following four steps: hazard identification, hazard characterization, exposure assessment and risk characterization (WHO/IPCS 2009; Domenech & Martorell, 2016).

When a carcinogenic chemical substance has been identified in food, hazard characterization generally considers that carcinogenic processes can be grouped into two major modes of action (MOA): the first is when the compound or its active metabolite reacts covalently with DNA (genotoxic), and the second when the action is epigenetic and produces tumours by a mechanism other than genotoxicity (non-genotoxic) (Gray & Collins, 2000; Loeb & Loeb, 2000). In the first case, there is a risk of cancer to humans at any level of exposure and therefore there is no safe exposure dose, i.e. there is no threshold dose. However, there is a threshold dose for non-genotoxic carcinogens, below which adverse effects are unlikely to occur (Dybing et al., 2002). This difference often determines not only the selection of the risk assessment methodology, but also risk characterization.

Inorganic arsenic (iAs) and lead (Pb) are both classified by the International Agency for Research on Cancer as probably carcinogenic to humans, Group 1 and Group 2A, respectively (IARC, 2020). Following the first toxicological studies, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable weekly intake (PTWI) as a threshold dose for each one. However, subsequent studies showed that uncertainty in the dose-response relationships and the observed adverse effects indicated that it was not appropriate to establish such a threshold dose (U.S. EPA, 2004; EFSA, 2009; EFSA, 2010).

For non-threshold carcinogens such as iAs and Pb the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the International Life Sciences Institute's European Branch (ILSI Europe) and EFSA (European Food Safety Authority) proposed the use of the margin of exposure (MOE) as an indicator of the level of public health concern (Barlow et al., 2006). The MOE is defined as the ratio between a reference point (RP) and the exposure dose to the carcinogen substance for a given population (US EPA 2012; EFSA, 2016; EFSA 2017).

The MOE can thus be used as a risk characterization metric and can help in making decisions on strategic risk management objectives, especially if it is accompanied by an appropriate narrative explaining the uncertainties inherent in the data (EFSA, 2005; Barlow et al., 2006; WHO/IPCS, 2009). The EFSA/WHO (2006) emphasized that the basis for decision-making should not be the MOE alone as it is only one component of the overall risk assessment and recommended a dialogue between risk assessors and risk managers to better interpret the implications of specific MOE magnitudes for human health.

In this context the aim of the present work was to introduce the fundamentals and formulation of the probability of exceedance (POE) metric, which provides complementary information to the MOE in risk characterization to support risk managers' decision-making. This metric is better suited to assessing public health risks than the MOE, particularly those of dietary toxic substances, which often have positively skewed intake distributions. A case study was included in which MOE and POE were calculated for iAs and Pb intake through the total diet in adults from five different countries.

2. Theory and calculation

This section compares the rationale and formulation of the POE and MOE metrics within the risk characterization framework.

2.1. Margin of exposure

The MOE is commonly calculated as the ratio between a RP, BMDL(*i,e,p*), and the estimated human exposure, EDI(*i*), which must include the uncertainty that may arise from the uncertainty in both EDI(*i*) and BMDL(*i,e,p*). A Pure Monte Carlo method may be used to propagate the variability from the inputs EDI(*i*) and BMDL(*i,e,p*) to the output to yield a *pdf* for MOE(*i,e,p*) by adopting Eq. (1).

$$\mathrm{MOE}(i, e, p) = \frac{BMDL(i,e,p)}{EDI(i)} \qquad (1)$$

Where, EDI(*i*) units are µg/kg-bw/day (µg per kg of bodyweight per day), which represents the overall exposure to hazard *i* across the entire diet (FAO/WHO, 2008). The BMDL (lower confidence limit of the BMD) is normally used rather than the BMD (benchmark dose) as a RP for risk characterization (EFSA, 2005, WHO/IPCS, 2009; US EPA 2012; EFSA, 2016; EFSA 2017). The BMD was introduced as an approximation to the dose-response relationship. It represents the exposure dose to the chemical (*i*) that produces a predetermined change in the response (*p*) of the adverse health effect (*e*). This predetermined change in the response is called the benchmark response (BMR) (Haber et al., 2018). Then, first, an increased response BMR must be defined, e.g. p=1%, which means that the incidence (response level) has increased 1% in relation to the background response. The BMDL ensures that the chosen BMR is not exceeded at a 95% confidence level (EFSA, 2016; Haber et al., 2018). The identified BMDL often ranges within an interval instead of being a single value because of the uncertainty involved in determining the BMDL process.

Fig. 1 represents the *pdf* of the EDI(i) distribution by a purple line, f(E), and E_m is the mean value of the EDI(i) distribution. The vertical green lines represent the reference point under the BMDL approach. Thus, if the BMDL is given by a single value, e.g. BMDL$(i,e,p)=D$ (solid green line), it represents the exposure dose at which there is a percentage increase in response not exceeding p, e.g. 1% at a 95% confidence level, in relation to an adverse health effect e, e.g. lung cancer, produced by ingesting a hazard i, e.g. iAs. Alternatively, the BMDL can be given in an interval range [D_1, D_2] (dotted green lines). For example, mean MOE could be calculated as the ratio D/E_m in Fig. 1.

In interpreting the results of the MOE (i,e,p), EFSA in (2005) proposed that for a genotoxic and carcinogenic compound, a value of 10,000 or more based on a $BMDL_{10}$ from an animal study would be of low concern from a public health point of view and could be considered as a low priority for risk management measures.

However, several proposals have been made for iAs, which does not appear to have direct genotoxicity but is rather a secondary effect. The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment agreed that a MOE of 10 or greater associated with 0.5% increased risk ($BMDL_{0.5}$) for lung cancer in humans could be considered of low concern in this case (COT, 2016). The Swedish National Food Agency (SNFA) developed a tool for comparing chemical risks associated with chronic exposure via food consumption (SNFA, 2015). It provided a risk classification approach that categorizes health concern levels. For iAs it proposed a relationship between risk class, level of health concern and the MOE associated with $BMDL_{0.5}$ for human lung cancer, which has been adapted in Table 1 to compare the MOE and the POE results in the case study.

For Pb, the EFSA Panel on Contaminants in the Food Chain considered cardiovascular and nephrotoxicity effects, with the associated 1% and 10%, increased BMR, respectively (EFSA, 2010). It concluded that MOE of 10 or greater is of negligible public health concern. However, at lower MOEs greater than one, the concern was considered to be very low for cardiovascular effects and nephrotoxicity, indicating that the risk of both effects cannot be discarded for MOEs lower than one.

2.2. Probability of exceedance

The probability of exceedance in the context of this manuscript is adapted from the general definition of a probabilistic margin in (Doménech & Martorell; 2016). Thus, Eq. (2) formulates the probability of exceedance, POE*(i,e,p)*, which implicitly includes uncertainty assessment arising from the uncertainty in both EDI(i) and BMDL(*i,e,p*). As with the MOE, a standard Monte Carlo method can be used to propagate the variability from the input distributions to obtain the variability in the POE.

$$\mathrm{POE}(i,e,p) = \Pr(\mathrm{EDI}(i) > BMDL(i,e,p)) = \int_{\mathrm{BMDL}(i,e,p)}^{\infty} f(E)\, dE \qquad (2)$$

The POE(*i,e,p*) represents the probability that exposure dose to a carcinogenic hazard, EDI(*i),* exceeds the BMDL(*i,e,p*). The result obtained after the quantification of POE(*i,e,p*) always ranges between zero and one. The red area in Fig. 1 represents the POE*(i,e,p)* result for the particular case of an RP given by a single value, i.e. D, which represents the area of the EDI(*i*) distribution that exceeds D.

The POE is thus a measure of the probability that the change in the response of the population exceeds the predefined BMR. It could be interpreted also as the fraction of total population exposed to increased risk. For example, using Table 1, for iAs it would provide an estimate of the fraction of the population exposed to risk class #1.

The POE*(i,e,p)* metric can thus be used as a measure of the level of concern, i.e. the higher the POE the greater the level. A POE value equal to zero would mean that EDI (*i*) never exceeds the suggested BMDL(*i,e,p*) and one can conclude that there is no concern with regard the background response of the population. A value of this metric close to zero would mean that EDI (*i*) almost never exceeds the suggested BMDL(*i,e,p*) and thus that the level of concern though not high cannot be disregarded. A value close to one would mean that exposure exceeds the RP with a high probability indicating a high level of concern.

3. Materials and methods

This section describes a case study and the data and method adopted calculate MOE and POE using the equations given above using data from five countries for total adult dietary intake of iAs and Pb.

3.1.Exposure data

Total diet studies (TDS) of Australian, Chinese, European, Japanese, and American adult populations were considered to assess exposure to iAs and Pb. These diets were chosen to include a variety of countries around the world with different exposure distribution function parameters, e.g. mean value, kurtosis coefficient, etc., to facilitate the subsequent discussion of the results.

Table 2 shows the mean and the 95th percentile of the exposure to iAs and Pb in total diet for each country, with the sole exception of Australia and the United States, for which the original sources give the Pb exposure value at the 90th percentile. The last column shows the exposure daily intake distribution functions used to carry out the case study. These EDI distributions are the result of adjusting the available data from the original source to a gamma distribution with @Risk 7.6 software (Palisade, Middlesex, UK) following Vilone et al (2014), who concluded that a gamma distribution is preferable to a normal distribution to fit food consumption.

3.2. Inorganic arsenic reference point

In 2010, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered epidemiological studies to suggest a lower benchmark dose confidence limit for a 0.5% higher incidence of lung cancer ($BMDL_{0.5}$) of 3.0 μg/kg-bw per day. However, a sensitivity analysis to investigate the impact of uncertainty in the exposure estimate of the reference study population to iAs in drinking water and food indicated that this $BMDL_{0.5}$ could be in the range of 2.0-7.0 μg/kg-bw per day (FAO/WHO, 2011; WHO, 2011a).

On the other hand, the EFSA panel on contaminants in the food chain suggested a $BMDL_{01}$ between 0.3 and 8 μg/kg-bw per day for a 1% higher incidence risk of cancer of the lung, skin, and bladder, as well as skin lesions (EFSA, 2009; ECHA, 2013). This expert group chose a 1% excess risk as these doses are likely to be within the range of exposures experienced by average and high-level European consumers.

Table 3 shows the RPs used in the application case for iAs, damage (LC= lung cancer; LSBC= skin, bladder, and lung cancer) and increased incidence ($BMDL_{0.5}$ and $BMDL_{01}$, respectively). Both were assumed to follow a uniform distribution, as this is the non-informative distribution that assumes that all outcomes are equally likely.

3.3. Lead reference point

In the absence of a health-based guidance value (HBGV), the EFSA (2010) proposed a $BMDL_{01}$ of 1.50 µg/kg-bw/day as RP for cardiovascular damage to systolic blood pressure in adults, and a $BMDL_{10}$ of 0.63 µg/kg-bw/day for nephrological damage causing chronic kidney disease in adults. All these values are listed in Table 4 and represent the RPs for Pb considered in the case study.

3.4.Method

A standard Monte Carlo method was performed to propagate the variability from the input distributions to obtain the variability in the MOE and POE distributions using Eqs (1) and (2) respectively. A total of 100,000 iterations per simulation were run using Latin Hypercube sampling. The simulation procedure was composed of the above data and equations as a spreadsheet model in Microsoft Excel, with add on @Risk 7.6 software (Palisade, Middlesex, UK).

4. Results and Discussion

4.1. Inorganic arsenic

The results of the MOE and POE metrics comparison with the $BMDL_{01}$ and $BMDL_{0.5}$, defined for dietary exposure to iAs and for each of the countries studied, are given in Table 5.

The highest mean MOE values were found in Australia, where mean MOE, in relation to BMDL (iAs, LSBC, 01) and BMDL (iAs, LC, 0.5), were 275.65 and 313.15, respectively. The mean EDI is therefore far from both RPs, which means that the level of concern was low in relation to both BMDLs for average adult consumers, according to the MOE interpretation criterion introduced in Section 2.1. The remaining countries had mean MOE values ranging from 21.09 to 46.65, one order of magnitude lower than those for Australia, which means that regardless of the chosen BMDL, the level of concern could be classified as low to moderate following the same criterion (Table 1).

Fig. 2 shows that the shape of the EDI distributions varied widely by country. The interpretation of the mean MOE leads to conclusions about the level of concern for dietary exposure to iAs of the average adult population. Conclusions need to be drawn about the level of concern in adult groups with high dietary exposure. The 5^{th} percentile MOE provides information on this group of adults from the 95^{th} percentile EDI with a dietary exposure to iAs.

The highest 5^{th} percentile MOE values were again found in Australia. Compared with BMDL (iAs, LSBC, 01) its 5^{th} percentile MOE was 10.89 and 24.50 (iAs, LC, 0.5), showing that the dietary exposure to iAs of this group of Australian adults was not so far from the RPs, which means the level of concern is in the low-to-moderate range in relation to both BMDLs for this group of adults according to the MOE criterion (Table 1). The MOE result at the 5^{th} percentile for the USA in relation to the BMDL (iAs, LSBC, 01) and BMDL (iAs, LC, 0.5) indicates a moderate-to-high and low-to-moderate level of concern, respectively.

The remaining countries obtained values ranging from 1.96 to 8.39, which implies a moderate-to high level of concern.

These MOE results were similar to those obtained by other authors in previous studies. The Centre for Food Safety conducted the First Hong Kong TDS and in relation to the BMDL (iAs, LC, 0.5) found that the MOEs ranged from 9 to 32 for the average Hong Kong population and from 5 to 18 for high consumers (CFS, 2012). The CFS concluded that the higher the MOE the lower the health concern and that efforts should be made to reduce the populations' exposure to iAs. In France, Chan-Hon-Tong et al., (2013) studied dietary pregnant women's iAs exposure and obtained a mean MOE of 1.2 in relation to $BMDL_{01}$=0.3μg/kg-bw/day and 33 in relation to $BMDL_{01}$=8, highlighting that these MOE values were too low to exclude risks as the exposures appeared to be of concern. In Italy, Cubadda et al., (2016) studied daily exposure to iAs, finding that the MOE relative to $BMDL_{01}$for average adult exposure ranged from 4 to 114 and the MOE for adult exposure at the 95th percentile ranged from 1 to 32. They also pointed out that efforts to reduce iAs dietary intakes were needed in general and not only for adults.

The 5th percentile MOE values ranging from 1 to 10 for some countries suggested that the highest EDI values in these countries may be very close to the RPs. This indicates the existence of a group of adults with very high dietary exposure to iAs, which could exceed the RPs and depends on the shape of the country's EDI distribution (see Fig. 2). The level of concern for this group would therefore be high, as the corresponding MOE would be less than one (Table 1). The use of the POE metric, which quantifies the probability of the EDI exceeding the BMDL, helps to draw conclusions about the role of this group of adult population with very high dietary exposure to iAs and the level of concern regarding the background response of the adult population.

The probability of the EDI exceeding the BMDL (iAs, LC, 0.5) was zero for all the countries, apart from Japan, where this probability was very low (Table 1). According to the POE interpretation criterion introduced in Section 2.2, in relation to the BMDL (iAs, LC, 0.5), in general, there was no concern regarding the background response of the adult population. The level of concern was very low for Japan, as only a 0.001 % of the adult population would be exposed to an increased risk in relation to the BMDL (iAs, LC, 0.5).

In contrast, the POE for the BMDL (iAs, LSBC, 01) was not zero for any country. It was very low for Australia and the USA, while it was low for China and the EU and not so low for Japan. The POE results provided extra information that complemented the 5th percentile of the MOE results. Thus, last three countries reached a similar 5th percentile of MOE (from 1.96 for Japan to 3.02 for China) in relation to BMDL (iAs, LSBC, 01), however, the corresponding mean Japanese POE was one order of magnitude higher than the Chinese and EU POEs, while the MOE (5th percentile) in the USA was 4.96, which was very close to the Chinese (3.02) and the EU (2.90), although the mean USA POE value was two orders of magnitude lower than the corresponding Chinese and EU values. These POE results can be seen in Fig 2, where only the EDI distribution for Australia and the USA were almost always below the BMDL (iAs, LSBC, 01).

Based on the POE interpretation criterion given in Section 2.2 and the results for $BMDL_{01}$, only 0.00036% of Australian and 0.004% of USA adults would be exposed to an increased risk in relation to the BMDL (iAs, LSBC, 01), so that the level of concern would be very low for both countries. In contrast, 0.145%, 0.171% and 1.42% of the adult population in China, the EU, and Japan, respectively, would be exposed to the increased risk in relation to the BMDL (iAs, LSBC, 01), so the level of concern would not be high but neither would it be low. Thus, the MOE at the 5th percentile in relation to the BMDL (iAs, LSBC, 01) for the EU (2.90) and Japan (1.96) were similar and the level of concern can be classified as moderate to high for both (Table 1). However, the POE results show a difference of one order of magnitude in relation to the adult population exceeding the response background in each country, 0.17% and 1.42%, respectively. The level of concern could therefore be interpreted as closer to moderate in the case of the EU and closer to high in the case of Japan.

4.2. Lead

Table 6 shows the MOE and POE results for the two types of health effects considered in the present study in relation to estimated daily Pb intake in total diet.

The results of the mean MOE for cardiovascular effect indicated that, according to the MOE criterion in section 2.1., dietary exposure to Pb of EU adults (4.94) can be considered of very low concern, while for the remaining countries (ranging from 13.95 to 61.18) it can be considered of no public health concern. In addition, the 5^{th} percentile of the MOE values obtained suggested that the level of concern in adult groups with high dietary exposure to Pb was of no concern for the USA (21.03), while it was of very low concern for this group of high consumers in the remaining countries (ranging from 1.27 to 9.67).

Similar results were found by the EFSA (2010), who, taking into account data of Pb concentrations in various food commodities and tap water from 2003 to 2009, assessed the Pb dietary exposure for average and high adults consumers across European countries and calculated the margin of exposure compared with the $BMDL_{01}$ (1.5 µg/kg-bw/day). The average consumer MOE was 1.2-4.2 and 0.62 - 2.1 for high consumers, indicating that the second population group's Pb could be a potential concern. On the other hand, the RIVM assessed the intake of Pb via food in the Netherlands, concluding that the MOEs for cardiovascular effects in adults were higher than one for median and 95^{th} percentile of exposure (3.7 and 2.1, respectively), considering that the risk of a cardiovascular effects was very low (NIPHE, 2017). Juric et al., (2018) carried out a risk assessment of dietary Pb exposure in Ontario (Canada) using a total diet study for the total population and found that mean MOE was 6.2 and 0.81 at 95th percentile, concluding that high consumers were exposed to a high risk of Pb toxicity. Higher values were found by Malavolti et al. in (2020) in assessing the dietary intake of Pb in the North of Italy and determined that the mean MOE was 7.7 and 4.4 for the 95th percentile, concluding that the effect on the systolic blood pressure due to Pb intake was of low concern.

According to the extra information provided by the POE metric (see also Fig. 3), the POE for Australia and the USA was zero and consequently, by the POE interpretation criterion given in Section 2.2, there would be no concern regarding the background response of the adult population to cardiovascular effects in these countries. On the other hand, the POE for EU and Japan, although not zero, was very low (over 1E-07), which means that the risk of this effect cannot be discarded for the small fraction of the adult population with a large dietary exposure to Pb. However, China presented the worse scenario, as about 1.84% of its adult population would be exposed to an increased risk of cardiovascular health effects due to dietary Pb intake. This suggested mean and 5th percentile of the MOE do not give the complete picture to draw conclusions about the possibility of having a greater response above the background and the level of concern. Thus, for example, the 5th percentile MOE for EU and China are quite similar, 1.81 and 1.27 respectively, but nevertheless China's POE is five orders of magnitude higher than that of the EU.

The results of the mean MOE for nephrotoxicity effect showed two groups. In the first the USA and Australia had MOE values higher than 10 (25.69 and 13.99, respectively), which would mean that dietary exposure to Pb in these countries can be considered of negligible public health concern in relation to nephrotoxicity effects, according to the MOE criterion given in Section 2.1. In the second group Japan, China and EU had values ranging from one to ten (7.9, 5.86 and 2.07, respectively), which would mean that dietary exposure could be considered of very low concern. In addition, the 5^{th} percentile of the MOE values obtained suggested that the level of concern in adult groups with high dietary exposure to Pb was very low for the USA, Australia and Japan (8.83, 4.06 and 1.97, respectively) in relation to nephrotoxicity. On the other hand, the 5^{th} percentile of the MOE values, which were lower than one for the EU and China (0.76 and 0.53, respectively) suggested that the risk of the nephrotoxicity effect cannot be discarded for these countries.

These results are quite similar to those published by other authors. The EFSA (2010) found that the average consumer's MOE was 0.51-1.8, considering that for the first value the possibility of an effect of Pb cannot be excluded. However, for values higher than one, the risk of nephrotoxicity could be considered low. In relation to high consumers the MOE ranges from 0.26 to 0.86, concluding that the possibility of a Pb effect should be considered of concern. In the same vein, NIPHE in (2017) reported that at the median exposure level the MOE in adults was 1.5, concluding that the risk of a nephrotoxicity effect was considered to be very low. However, for high consumers it was 0.9, concluding that the health risks to the kidney of long-term exposure to Pb cannot be excluded.

On the other hand, the POE obtained for Australia and the USA was zero and consequently, there would be no concern for the background response of the adult population to nephrotoxicity in these countries, which confirms the conclusions obtained when the mean MOE was considered. Moreover, the POE for China and the EU revealed that about 25% of their adult population would be exposed to an increased risk in relation to nephrotoxicity due to dietary Pb intake. This again confirms the conclusions obtained when the 5^{th} percentile of the MOE was considered. However, again, the mean and 5^{th} percentile of the MOE did not show the full picture. For example, the 5^{th} percentile MOE for Japan was 1.97, which suggested a very low level of concern according to this criterion, but nevertheless Japan's POE result suggested that about 0.2% of its adult population would be exposed to an increased risk regarding the background response for nephrotoxicity.

5. Concluding remarks

The POE metric complements the information provided by the MOE metric permitting an improved risk characterization. One of the main advantages of the POE metric is that it considers the whole EDI distribution when considering the percentage of the population that exceeds the RP and therefore has a risk above the pre-established risk for the background population response. The POE metric is thus especially appropriate for characterising public health risks when the distribution of the estimated daily intake of a non-threshold chemical hazard is positively skewed and thus helps to draw risk-informed conclusions about the level of concern regarding the BMDL.

The case study carried out on iAs and Pb numerical data showed how similar MOE values and consequently similar levels of concern, had different probabilities (i.e. POE) of having an increased background risk of suffering an adverse health effect. In short, the POE made it possible to nuance the level of concern and to provide information on the risk of dietary exposure to iAs and Pb, so that risk managers can act accordingly to reduce the level of concern and the increased risk of adverse health effects using both MOE and POE information.

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Fig. 1. Key concepts in formulating the POE metric defined for a chemical hazard (i), an effect (e) a predetermined change in the response BMR (p), where f(E) is the probability density function of the daily intake distribution EDI(i); Em is the mean EDI value, BMDL(benchmark dose lower confidence limit) at 5th, 50th and 95th percentile, (D1, D and D2,respectively) and POE is the probability of exceedance (red area under the f(E) curve) that exceeds the reference point (in this case the mean BMDL, D)

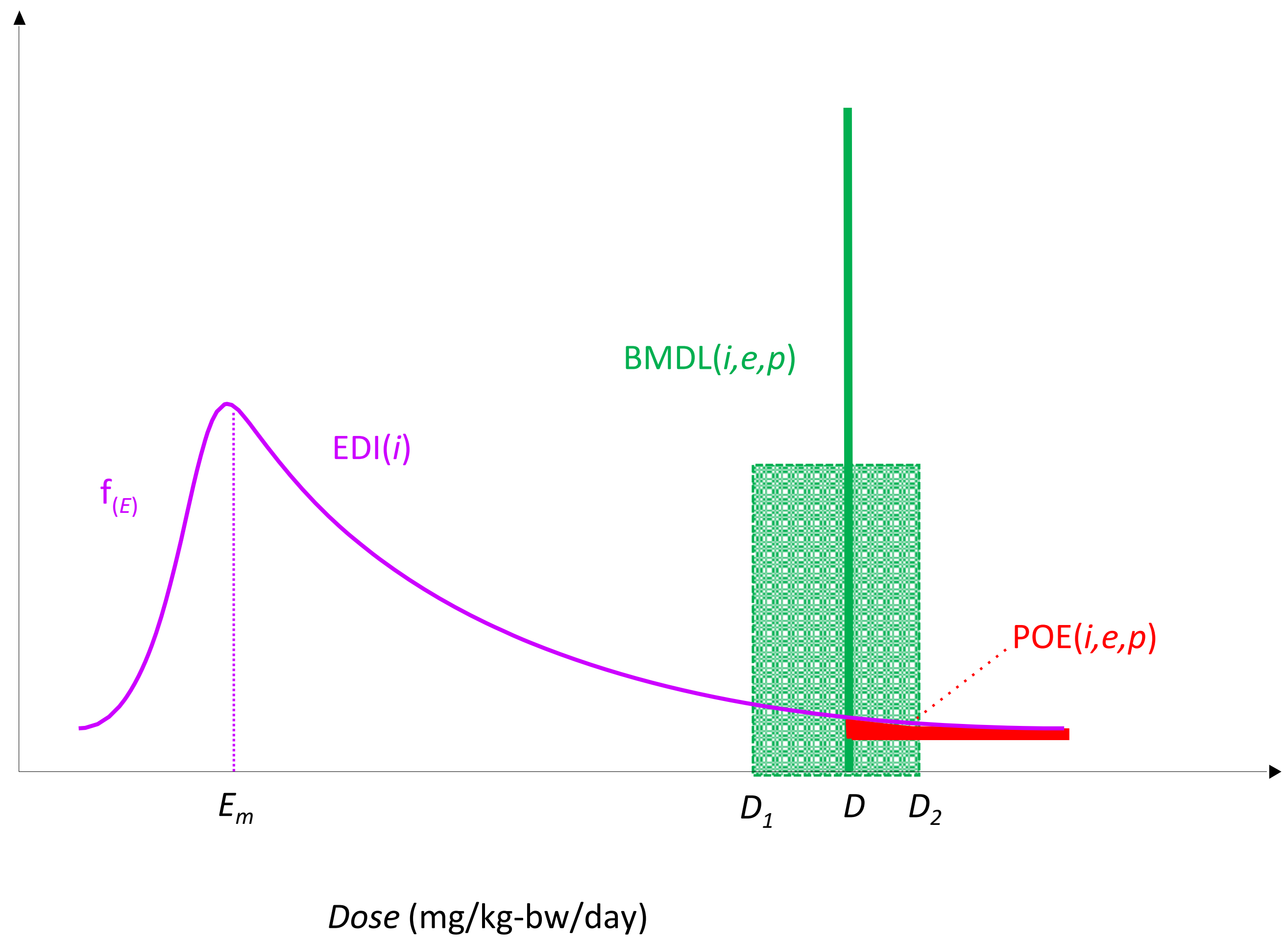

Fig. 2. Key concepts in formulating the POE metric defined for a chemical hazard (*i*), an effect (*e*) a predetermined change inthe response BMR (*p*), where $f_{(E)}$ is the probability density function of the daily intake distribution EDI(*i*); E_m is the meanEDI value, BMDL (benchmark dose lower confidence limit) at 5^{th}, 50^{th} and 95^{th} percentile, (D_1, D and D_2, respectively) and POE is the probability of exceedance (red area under the $f_{(E)}$ curve) that exceeds the reference point (in this case the mean BMDL, *D*).

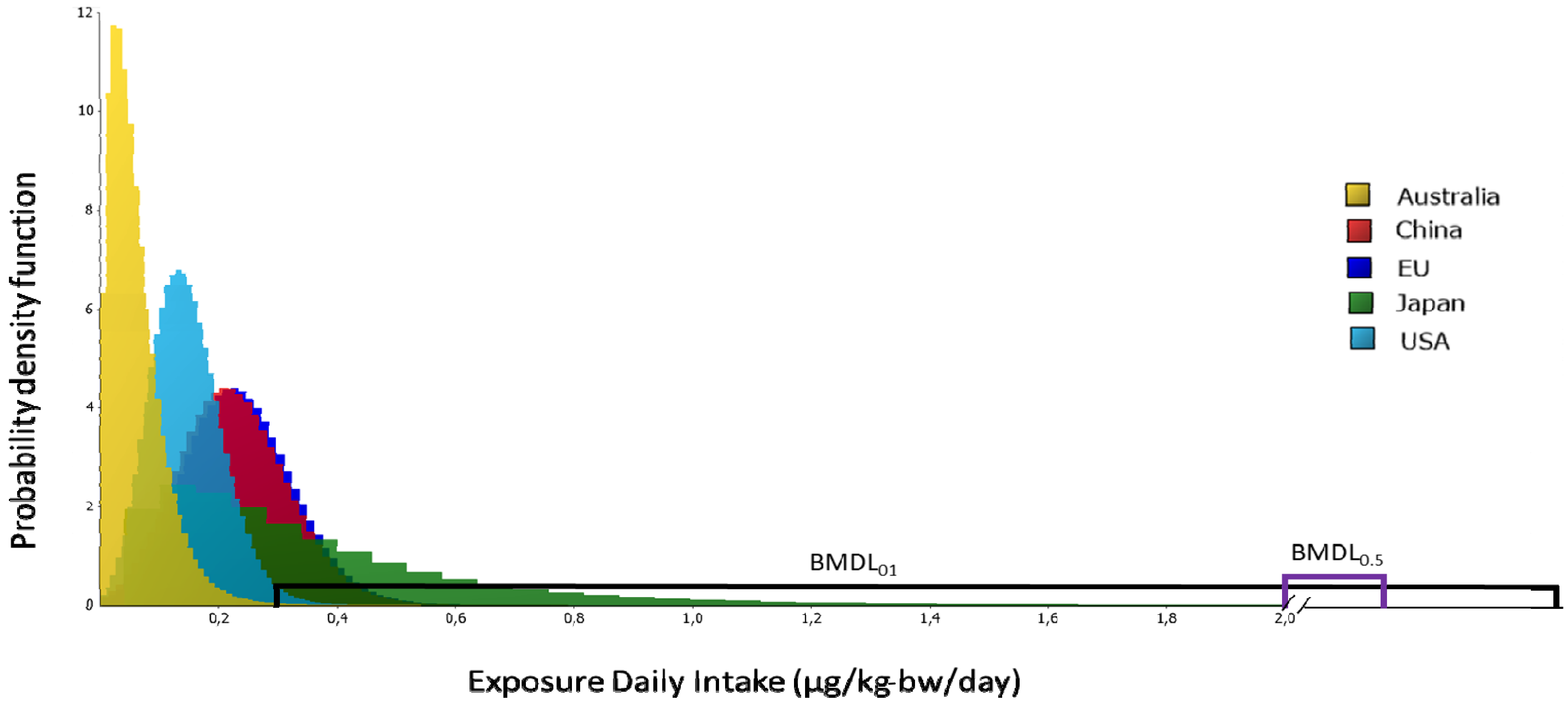

Fig. 3. EDI probability density function for iAs in different countries and two BMDLs as reference points: BMDL0.5 for 0.5% increase in response to having lung cancer (2-7µg/kg-bw per day), and BMDL01 for 1% increase in response to having lung, bladder or skin cancer (0.3-8 µg/kg-bw per day)

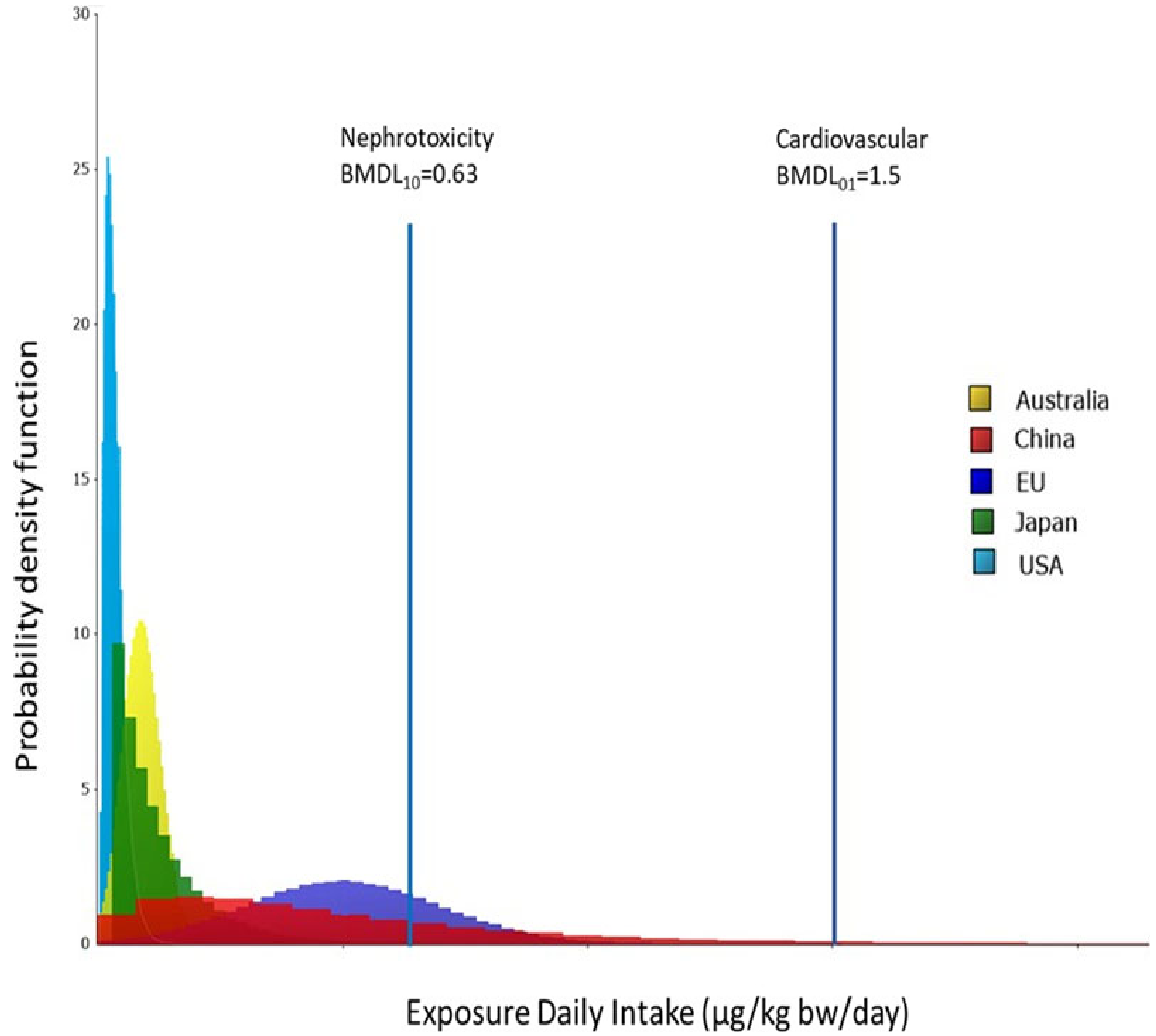

Fig. 4. EDI probability density function for Pb in different countries and BMDL01 for 1% increase in response for cardiovascular effect and BMDL10 for 10% increase in response for nephrotoxicity.

Table 1. Relationship between risk class, level of health concern and MOE associated with $BMDL_{0.5}$ for lung cancer in humans exposed to iAs in food. Adapted from (SNFA, 2015)

Risk class	**Concern level**	**MOE**
1	High	< 1
2	Moderate-to-high	1 – 10
3	Low-to-moderate	10 – 100
4	No-to-low	100 – 1000
5	No	> 1000

Table 2. Adult exposure values to iAs and Pb (µg/kg-bw per day) in total diet for various countries

Metal	Study Country	Mean exposure (µg/kg-bw/day)	95th percentile (µg/kg-bw/day)	Source	EDI distribution function (5th, 50th, 95th percentile)
iAs					
	Australia	0.049	0.12 (90th)	FSANZ, 2019	Gamma (0.008;0.05;0.15)
	China (Hong Kong)	0.22	0.38	Wong et al., 2013	Gamma (0.08;0.22;0.38)
	EU	0.23	0.39	EFSA, 2014	Gamma (0.09;0.23;0.39)
	Japan	0.315	0.754	FSCJ, 2013	Gamma (0.07;0.27;0.83)
	USA	0.14	0.25	WHO, 2011a	Gamma (0.05;0.14;0.25)
Pb					
	Australia	0.089	0.14 (90th)	FSANZ, 2019	Gamma (0.03;0.089;0.15)
	China (Guangzhou)	0.37	1.18	Wang, et al., 2019	Gamma (0.06;0.376;1.18)
	EU	0.5	0.83	EFSA, 2012	Gamma (0.18;0.5;0.83)
	Japan	0.095	0.319	Hayashi et al., 2018	Gamma (0.04;0.096;0.31)
	USA	0.03	0.06 (90th)	WHO, 2011b	Gamma (0.01;0.03;0.07)

Table 3. Case study reference points: BMDL, defined for inorganic arsenic (iAs), type of damage (LC =lung cancer and LSBC=skin, bladder and lung cancer) and increased incidence (0.5% and 1%)

BMDL	Range of values (μg/kg-bw/day)	Damage	Source	Reference Point
BMDL(iAs, LC, 0.5)	2-7	Lung cancer (LC)	FAO/WHO, 2011	Uniform (2;7)

Table 4. Case study reference points: BMDL, defined for lead (Pb), type of damage (CV=Cardiovascular, NP=Nephrotoxicity) and the increased incidence (1% and 10%)

BMDL	Reference Point (μg/kg-bw/day)	Damage	Source
BMDL(Pb, CV, 01)	1.5	Cardiovascular	EFSA, 2010
BMDL(Pb, NP, 10)	0.63	Nephrotoxicity	EFSA, 2010

Table 5. MOE and POE results for inorganic arsenic (iAs) in five countries for two reference points: BMDL(iAs, LSBC, 01)=0.3-8 μg/kg-bw per day (EFSA, 2009) and BMDL(iAs, LC, 0.5)=2-7 μg/kg-bw per day (WHO, 2011a). Where LSBC=skin, bladder and lung cancer, LC=lung cancer and 0.5 and 01=increased incidence 0.5% and 1%, respectively

Country		MOE			POE	
	RP	5th	Mean	95th	Mean	Deviation
Australia	BMDL(iAs, LSBC, 01)	10.89	275.65	532.24	3.60E-06	2.21E-06
	BMDL(iAs, LC, 0.5)	24.50	313.15	554.27	0	0
China	BMDL(iAs, LSBC, 01)	3.02	36.48	59.62	1.45E-03	4.25E-05
	BMDL(iAs, LC, 0.5)	8.39	36.91	58.70	0	0
EU	BMDL(iAs, LSBC, 01)	2.90	27.33	54.50	1.71E-03	4.67E-05
	BMDL(iAs, LC, 0.5)	8.12	29.28	53.17	0	0
Japan	BMDL(iAs, LSBC, 01)	1.96	21.09	67.04	1.42E-02	8.86E-05
	BMDL(iAs, LC, 0.5)	4.39	22.87	66.07	1.08E-05	3.61E-06
USA	BMDL(iAs, LSBC, 01)	4.69	42.93	92.02	4.03E-05	6.85E-06
	BMDL(iAs, LC, 0.5)	12.92	46.65	90.03	0	0

Table 6. MOE and POE results for lead (Pb) in five countries for cardiovascular damage (CV) and nephrotoxicity (NP). Where, 01 and 10 are the increase incidence 1% and 10%, respectively

Damage/Reference point	Country	MOE			POE	
		5th	Mean	95th	Mean	Deviation
Cardiovascular	Australia	9.67	33.30	49.60	0	0
	China	1.27	13.95	25.18	1.84E-02	0
BMDL (Pb, CV, 01) =1.5 μg/kg-bw/day	EU	1.81	4.94	8.04	5.00E-07	5.27E-07
	Japan	4.70	18.82	42.86	3.00E-07	4.83E-07
	USA	21.03	61.18	140.70	0	0
Nephrotoxicity	Australia	4.06	13.99	20.83	0	0
	China	0.53	5.86	10.58	2.55E-01	0
BMDL (Pb, NP, 10) =0.63 μg/kg-bw/day	EU	0.76	2.07	3.38	2.58E-01	4.83E-07
	Japan	1.97	7.90	18.00	2.08E-03	5.16E-07
	USA	8.83	25.69	59.09	0	0