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Quantification and feed to food transfer of total and inorganic arsenic from a commercial seaweed feed

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ABSTRACT

Seaweed has a long-associated history of use as a supplemented livestock feed, providing nutrients and vitamins essential to maintaining animal health. Some species of seaweed, particularly the fucoids, are well-known accumulators of the metalloid arsenic (As). Arsenic toxicity to humans is well established even at low exposure levels and is considered a class 1 human carcinogen. As mankind's appetite for livestock produce continues to grow unabated, there is a concern that consumption of livestock produce reared on a diet supplemented with seaweed animal feed (SAF) may pose a threat to the human population due to potentially high levels of As present in seaweed. To address this concern and provide end users, including industry, consumers, policymakers and regulators with information on the exposure associated with As in commercial seaweed animal feed, the estimated daily intake (EDI) of As was calculated to evaluate potential human exposure levels. Using As data from a commercially available seaweed meal over a five-year period (2012–2017) a population exposure assessment was carried out. A Monte Carlo simulation model was developed to characterise the feed to food transfer of As from animal feed to animal produce such as beef, milk, chicken, and eggs. The model examined initial levels in seaweed, inclusion rate in animal feed, animal feeding rates and potential transfer to food produced from a supplemented diet of SAF. The analysis of seaweed animal feed showed that inorganic As was a small fraction of the total As found in seaweed meal (80:1). Statistical analysis found significant differences in the concentration of As in seaweed animal feed depending on the grain size ($p < 0.001$), with higher As concentrations in smaller sized grain fractions. Due to several detoxification steps and subsequent rapid excretion from the bodies of livestock, a very low carryover rate of As compounds from seaweed animal feed into livestock produce was observed. The EDI calculated in this study for the livestock produce evaluated at the 95th confidence interval was < 0.01% of suggested safe levels of inorganic As intake. The threat to the general population as a result of consumption of livestock products reared on a diet consisting of SAF is found to be negligible.

1. Introduction

Consumption of livestock and livestock produce contribute 12.9% of global calories and 27.9% of global protein through the provision of meat, milk, eggs, and offal (FAO, 2011). In response to population growth and subsequent food demand, global livestock production is forecasted to increase by 60–70% by 2050 (UN, 2007; Makkar et al., 2015). It is important, therefore, that care is taken in the provision of safe animal feed. The global animal feed market is currently valued at $460 billion and equates to a total annual global production of 980 million tonnes, with 439 million and 184 million tonnes produced for poultry and cattle, respectively (Alltech, 2015). The most recent surveys indicate that the global production of animal feeds has surpassed 1 billion tonnes (Alltech, 2016).

The global seaweed animal feed (SAF) market is worth $11.34 billion annually and accounted for roughly 2.5% of the global animal feeds market in 2016. Conservative estimates of the current value of the seaweed industry are US $10.1–16.1 billion, with projections of market growth to reach US $17.6 billion by 2021 (White and Wilson, 2015; Marketsandmarkets, 2016). Seaweed animal feed can play an important role in the diet of livestock as it is rich in amino acids, trace elements, antioxidants, and vitamins, while also assisting in nutrient absorption

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(Rey-Crespo et al., 2014). The brown seaweed *Ascophyllum nodosum* (Linnaeus) Le Jolis is the main algal species used for the production of livestock feed in Europe and North America and is exported globally to markets in Asia, Australia and South America (Makkar et al., 2015; Mac Monagail et al., 2017).

The benefits of seaweed inclusion in the animal diet are well documented (Brown et al., 2014). However, the production of seaweeds suitable for animal feeds are not without issues; for instance, the uptake of metals from the surrounding water is a phenomenon characteristic of seaweeds (Utomo et al., 2016) and *A. nodosum* has been widely used as a biomonitor of metal contamination in the marine environment (Morrison et al., 2008). Brown seaweeds, in particular, have a tremendous capacity to accumulate As (As being enriched in *Laminaria* species by a factor 200–500 compared with As in terrestrial plant material) (Morrison et al., 2008; Ratcliff et al., 2016). Weathering of As-containing rocks liberates inorganic forms of As, namely arsenic trioxide, arsenite, and arsenate, and is considered a major natural source of As distribution in the ocean (Ryan et al., 2015). The most common inorganic arsenic (As_{Inorg}) species in seawater is arsenate, with typical levels of $1.5\,\mu g\,L^{-1}$ found (range: $1–2\,\mu g\,L^{-1}$) (Smedley and Kinniburgh, 2002).

Total arsenic (As_{Tot}) is the most commonly recorded As value in the scientific literature. However, having little toxicological significance due to its ill-defined toxicity, it is difficult to draw conclusions from an As_{Tot} value (Petursdottir et al., 2015). Speciation information provides defined information on the potential risks associated with consumption of certain products. In isolation, As_{Tot} is not an adequate tool to use in the exposure assessment of As and one cannot infer adequate information on As toxicity and bioavailability as a result. In seaweeds, over 100 major As species, including organobetaine, organochlorine and a number of dimethylarsinyl riboside derivatives of organosugars have been identified (Andrewes et al., 2004; Francesconi, 2010; Navas-Acien et al., 2011). Compounds of As vary in toxicity with inorganic arsenic (As_{Inorg}) considered more toxic than organic species (As_{Org}) (Brandon et al., 2014). Organoarsenicals present in seaweeds, and other marine organisms are loosely considered nontoxic (Niegel and Matysik, 2010). The metabolism of arsenosugars in humans is, however, inherently dependent upon the metabolism of the individual (Feldmann and Krupp, 2011) and caution should be exercised when considering the toxicity of arsenosugars.

It was important to determine the potential human exposure to As as a result of consuming livestock meat, milk, and eggs as "any risk assessment of undesirable substances in feeds needs to consider the occurrence and exposure for consumers of these animal-derived products" (Dorne and Fink-Gremmels, 2012). Humans are routinely exposed to As in the environment via consumption of food and drinking water (Hughes et al., 2011; Morrison et al., 2016; Davis et al., 2017; McGrory et al., 2017; Monrad et al., 2017). Debate and ambiguity, however, surrounds the determination of acceptable exposure levels for various As compounds (Gentry et al., 2014). Inorganic arsenic is categorised as a Group A human carcinogen by the United States Environmental Protection Agency (USEPA), and a Class 1 carcinogen by the International Agency for Research on Cancer (IARC) (Straif et al., 2009). The strong affinity for As uptake, coupled with the perennial growth of fucoids may result in its accumulation at elevated concentrations proving potentially hazardous to human health (Hwang et al., 2010). Limits on As_{Inorg} in seaweeds for human consumption vary globally. In France, the maximum allowable level of As_{Inorg} in food is $< 3.0\,\mu g\,g^{-1}$, while in Australia and New Zealand a limit of $1\,\mu g\,g^{-1}$ is in place (Mabeau and Fleurence, 1993; ANZFA, 2013). In animal feed, the maximum allowable concentration under European regulations is set at $40\,\mu g\,g^{-1}$ for As_{Tot} and $2\,\mu g\,g^{-1}$ for As_{Inorg} (Commission Regulation (EU) 2015/186) (EU, 2015). Historical incidences of mycotoxin (*Fusarium*) contamination of animal feeds (Coffey et al., 2009) has drawn worldwide attention to the animal feeds industry and has resulted in increased scrutiny (Binder et al., 2007; Antonissen et al., 2014; Zachariasova et al., 2014). Although meat (beef and chicken), milk and eggs are widely consumed, to the best of the authors' knowledge no human exposure assessment or estimation on As in seaweed animal feed has been undertaken. Therefore, this study aims to improve our understanding of the potential human exposure to As associated with the consumption of livestock (livestock products) raised on *A. nodosum* animal feed. The exposure to As by the studied population from consumption of bovine and poultry produce fed SAF was estimated. A Quantitative Exposure Assessment (QEA) methodology was used to assess the probability and severity of potential As transfer to humans. This exposure assessment will provide end users including industry, consumers, policymakers, and regulators with information on the exposure levels associated with As in commercial seaweed animal feed and evaluate the provision of safe animal feed, addressing seaweed quality issues.

2. Materials and methods

2.1. Seaweed animal feed (SAF)

For the purpose of this study, any reference made to beef, poultry, milk or eggs refers to those commodities, which have been produced from a diet consisting of SAF. Fig. 1 highlights the basic transport route of As into humans from SAF.

The data used in this study originated from the monthly monitoring and testing of total and inorganic As in a commercial, internationally available SAF (*A. nodosum*) between January 2012 and February 2017. During this period, total As was determined in 62 feed batches, and inorganic As in 60 batches (As_{Tot} $n = 62$; As_{Inorg} $n = 60$) in two different grain size fractions of the SAF (Small Grain (SG); 850–250 μg) and Large Grain (LG); 1940–850 μg).

2.2. Study area and sample preparation

The location from which *A. nodosum* was harvested for the production of SAF extends from 54° 20′ 58.8732″ N, 9° 48′ 2.592″ W to 53° 11′ 50.3772″ N, 8° 59′ 25.7244″ W over a 1000 km stretch of the Atlantic coastline of Ireland. The intertidal lithologies from these harvesting areas comprise igneous, sedimentary and metamorphic bedrock types (Hepworth Holland and Sanders, 2009; Morrison et al., 2009; Guiry and Morrison, 2013). The study area contains a comparatively low human population density with relatively little heavy industry and subsequent low inputs of wastes into the coastal water (Morrison et al., 2008; Morrison et al., 2017; Wilkes et al., 2017).

Harvested *A. nodosum* is dried before being industrially milled via sieving through multiple screens (ranging from < 250 to 1940 μm) where it is processed into animal feed and exported worldwide.

2.3. Determination of total and inorganic arsenic

On a monthly basis between 2012 and 2017, dry feed samples (~0.5 kg) of LG-SAF and SG-SAF were collected at random positions form three bags of SAF product from a commercial producer in Ireland. All the samples were analysed in the GAFTA (The Grain and Feed Trade Association) approved laboratory (TLR, Netherlands) for the determination of organic and inorganic As fulfilling the requirements of the standard NEN-EN-ISO/IEC 17025:2005. A test portion of 0.3 g of dry feed sample was treated with diluted nitric acid (CARLO ERBA, RS-Superpure for trace analysis, Cornaredo, Italy) and hydrogen peroxide (TraceSELECT® Ultra Sigma-Aldrich, USA) in a heated water bath. Hereby, the As species are extracted into solution and As(III) is oxidized to As(V). The inorganic As is selectively separated from other As compounds using anion exchange high-performance liquid chromatography (HPLC) (Thermo Scientific Dionex UltiMate3000) coupled online to the element-specific detector inductively coupled plasma - mass spectrometry (ICP-MS) (Thermo Scientific X Series II) for the

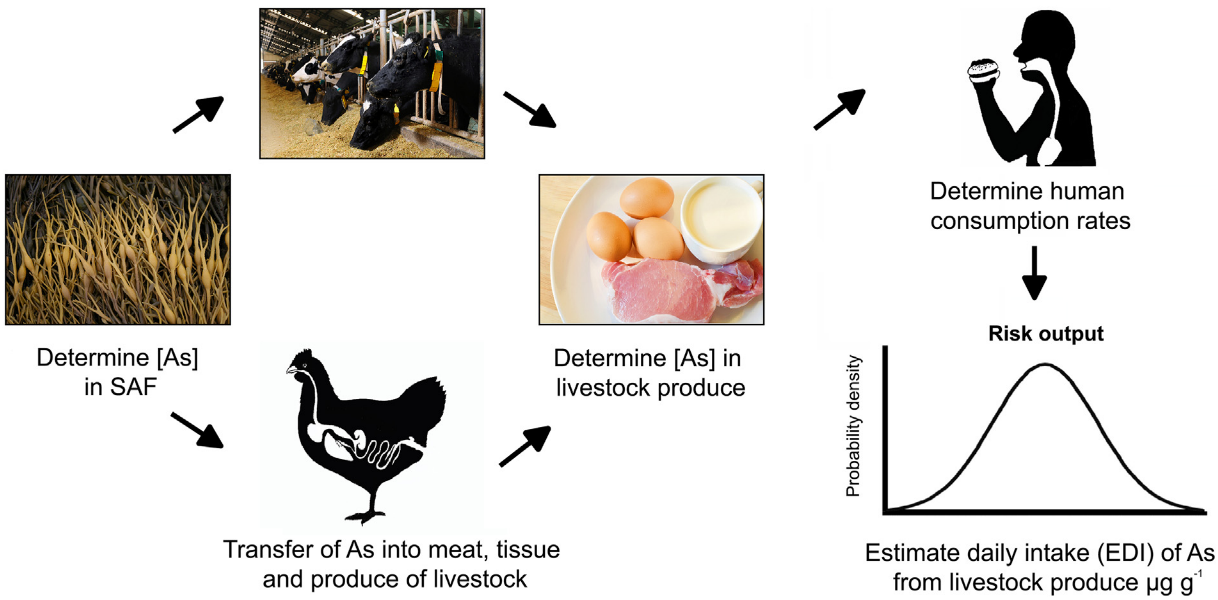

Fig. 1. Model schematic used to estimate the daily intake of arsenic from livestock produce consumption.

Table 1
Determination of arsenic species in the Certified Reference Materials (CRMs) of CRM 7405a (Hijiki) (National Metrology Institute of Japan [NMIJ]) using HPLC-ICP-MS [$\mu g\, g^{-1}$].

Element	Certified value (+SD)	Observed this study (+SD)	Recovery (%)
As_{Tot}	35.8 ± 0.9	35.7 ± 0.9	99.7
AsIII	10.1 ± 0.05	10.2 ± 0.04	101.1

determination of the mass fraction of inorganic As. The limit of quantification (LOQ) of the ICP-MS methods are as follows: As_{Tot}, 0.07 $\mu g\, g^{-1}$ (ICP-MS) and AsInorg 0.04 $\mu g\, g^{-1}$ (HPLC-ICP-MS), both based on wet weight of sample. Trueness and precision of analyses were insured by comparison with certified reference materials (Table 1). The measured concentrations of As were within the certified range. Both feed samples and CRMs were analysed for both inorganic and organic As. Any samples below the LOD were taken as equal to 0 $\mu g\, g^{-1}$. For total As in SAF, the solution, obtained by pressure digestion (ISO 13805) (CEM, MARS 6, USA), was nebulised and the aerosol transferred to a high frequency inductively coupled plasma mass spectrometer (ICP-MS). TLR uses The European Standard (EN 15763) for the determination of As in foodstuff and another method for feed which is based on EN 15763.

2.4. Data input; level of arsenic in seaweed animal feed

A summary of model inputs for estimating daily intake of As is shown in Table 2.

To model the concentration of As_{Tot} in SAF (As_{Con}) a best-fit distribution was applied to the monitoring data (Supplementary information (SI) Sheet 1 Tables S1 and S2) resulting in a lognormal distribution (mean 27.87 $\mu g\, g^{-1}$, Standard deviation 4.99 $\mu g\, g^{-1}$). A Pearson distribution with alpha equal to 6.87 $\mu g\, g^{-1}$ (shape parameter) and scale parameter beta equal to 3.23 $\mu g\, g^{-1}$ was used to model the concentration of As_{Inorg} also based on a best-fit to monitored data (SI Sheet 1 Tables S3 and S4). Information on As concentrations in SAF are summarised in SI Sheet 2 Figs. S1 and S2. Both figures represent the uncertainty in the levels of As in SAF and illustrate the spread of all possible concentration values based on monitoring data.

2.5. Data input; inclusion and feeding rates

The inclusion rate (Ir) of SAF into feed was determined from manufacturer's guidelines and are presented in Table 3, while information on livestock feed rates (Fr) were taken from published literature (Table 4).

2.6. Data input; biotransfer factors

It was possible to utilise a biotransfer factor (BTF) to estimate the transfer of As from feed to both beef and poultry meat and their co-products (Table 5). Biotransfer factors are defined as the ratio of the concentration of a chemical in animal tissues such as beef, poultry, milk or eggs, to the animals daily intake of that chemical (Dowdy et al., 1996). The carry-over rate or BTF of potentially toxic substances to livestock produce is determined via specific toxicokinetic limitations of mammalian and poultry meat (and their by-products). These specific limitations are dependent upon the absorption, distribution, metabolism, excretion rate and eventual metabolites of As once ingested (Dorne and Fink-Gremmels, 2012; Lopez-Alonso, 2012). The use of BTFs is a widely used and accepted method of estimating chemical transfer from contaminated vegetation into agricultural food products (USEPA, 2005). Information on the model distributions are summarised in SI Sheet 3 Table S5 and are based on empirical data. In this study, a best-fit distribution model was applied to assess human exposure to As from consumption of livestock produce. Although the absorption of As_{Org} and As_{Inorg} in the gastrointestinal tract of animals is variable but shown to be high (40–100% for As_{Org} and 60–100% for As_{Inorg}) (Hopenhayn-Rich et al., 1993; NRC, 2005; Nabrzyski, 2006; Vitousek et al., 2008), for the purpose of this study, it was assumed the bioavailability of As in livestock produce to humans was 100%.

2.7. Data input; human dietary intake

To assess the potential human dietary exposure to As, human dietary consumption data (kg day^{-1}) must be combined with occurrence data (i.e. As concentration in food) (Dorne et al., 2009). The dietary exposure to As is a consequence of the type and abundance of food consumed, and consumption estimates were used to determine the exposure levels to humans. A Lognormal distribution was used to characterise the consumption of different food produce based on national consumptive data from the Irish Universities Nutrition Alliance (IUNA, 2001; IUNA, 2011) (SI Sheet 3 Table S6).

Table 2
Model inputs for estimating daily intake of arsenic.

	Model input		Units	Reference
Seaweed animal feed	Concentration of arsenic in SAF	As_{Con}	Concentration of X or Y[a]	SI Sheet 2 Figs. S1 & S2
	SAF inclusion rate in feed	Ir	As per manufacturers guidelines	Table 3
	Livestock feeding rate	Fr	Feeding rate based on A, B, C, D[a] recommendations	Table 4
	Level of arsenic present in total feed	Lf	$As_{Con} \times Ir$	
	Arsenic concentration in ingested feed	$Feed_{Con}$		
Biotransfer	Biotransfer factor	BTF	Species dependent	Table 5, SI Sheet 3 Table S5
	Arsenic concentration in livestock produce	LS_{As}	$Lf \times Fr$	
Human exposure	Human intake of livestock produce	HI	Based on literature	SI Sheet 3 Table S6
	Body weight	BW	Based on literature	
	Exposure	EXP	$LS_{As} \times HI$	
	Estimated daily intake	EDI	$EXP \div BW$	Tables 6a & 6b

[a] Where X = As_{Tot} and Y = As_{Inorg}. A = poultry. B = eggs. C = beef. D = milk.

Table 3
Inclusion rate of SAF into livestock diets and total feed of livestock.

	Poultry	Eggs	Beef	Milk	Units	References
Recommended inclusion rate (Ir) of SAF into feed	2.5[a],[1]	–	100–120[b],[1]	120–150[c],[1]	g/day	(1) http://www.arramara.ie/
Inclusion rate (Ir)	0.025	0.025	0.105	0.125	$kg_{seaweed}/kg_{feed}$	As per manufacturer guidelines
Fr (feeding rate)	0.11	0.11	18–20	18–20	kg_{feed}/day	As per manufacturer guidelines

[a] Recommended feeding rate 25 kg per tonne of meal.
[b] Recommended 100–120 g per day beef cows.
[c] Recommended 120–150 g per day dairy cow.

Table 4
Livestock feeding inputs.

Livestock	Recommended total feed per day	Units	Reference
Chicken	0.113[1]	kg feed day^{-1}	(1) Jacob and Pescatore (2012)
	0.027[2]	kg feed day^{-1}	(2) NRC (1966)
	0.125[2]	kg feed day^{-1}	(3) Wiseman (1987)
	0.04[3]	kg feed day^{-1}	(4) Kavanagh (2015)
	0.13[3]	kg feed day^{-1}	(5) Hickox (2000)
			(6) McKone and Ryan (1989)
Beef cow	6.75–15.75[4]	kg feed day^{-1}	(7) Agricultural Research Council (1965)
	4.8–14.1[5,2]	kg feed day^{-1}	
	6.1–17.5[6]	kg feed day^{-1}	
	12.2[6]	kg feed day^{-1}	
	6.9[7]	kg feed day^{-1}	
	8.4–12.3[7]	kg feed day^{-1}	
	8.0[7]	kg feed day^{-1}	
Dairy cow	16.0–18.0[4]	kg dm day^{-1}	
	0.4–15.5[5]	kg feed day^{-1}	
	15.0–25.0[6]	kg feed day^{-1}	
	16.9[6]	kg feed day^{-1}	
	6.5[7]	kg feed day^{-1}	
	11.2[7]	kg feed day^{-1}	
	15.9[7]	kg feed day^{-1}	
	16.0[7]	kg feed day^{-1}	

2.8. Data input; body weight of cattle and humans

According to the Department of Agriculture, Food and the Marine (DAFM, 2015) the reported body weights of both Irish dairy cows and of beef cattle ranged from 205 kg to 527 kg for adult dairy cows, and from 241 kg to 537 kg for adult beef cattle (average of summer and winter weights; type of diet not listed). These weights were used to determine average feed requirements of cows. For human adult weight estimation, a Lognormal distribution was used, with a mean of 81 kg ± 13.1 kg based on dietary information from IUNA (2001).

2.9. Statistical analysis

A paired *t*-test was performed to assess differences in total and inorganic As concentration between the two grain sizes used for SAF. Statistical analyses were performed using the software R version 3.2.1 (R Development Core Team, 2017). In all statistical analyses, significance was set at p-value < 0.05 probability.

2.10. Model simulation

A Monte Carlo simulation model was developed to assess the estimated daily intake (EDI) of As by human adults. Monte Carlo simulation is a statistical model, which selects random values from distributions to produce multiple random scenarios of a problem while accounting for the natural uncertainty and variability in the input data (Schuhmacher et al., 2001). From the generated output, it is possible to produce a probability distribution using multiple scenarios of a problem. To develop the exposure model, the @RISK, version 4.0 (Palisade, USA), in combination with Microsoft Excel 2016 (Microsoft, USA) was used to run the simulation. The model was run for 10,000 iterations reflecting the high variability in the transfer of As to livestock products, including the inherent differences in human and animal consumption practices. The estimated level of As in livestock produce (SI Sheet 3 Table S7) and the probability of human exposure to As (Tables 6a & 6b) were outputs of the mathematical exposure model.

3. Theory - ambiguity regarding arsenic toxicity in seaweed

Much of the ambiguity regarding As toxicity in seaweed lies in the pervasiveness of naturally occurring As species in seaweed, the high number of secondary metabolites and the vast range of toxicities displayed by As. The potential toxicity of As in SAF is a function of the concentration of As in seaweed at the time of harvesting, the inclusion rates of SAF in the diets of livestock, the subsequent transfer of As via human consumption of animal produce and finally the chemical form As is present in (e.g. trivalent As(III) is the most toxic form of As).

Table 5
Reported biotransfer factors used in this study.

	Poultry BTF	Egg BTF	Beef BTF	Milk BTF	Reference
	0.02[5]	0.26[3]	0.002[9]	0.00011[1]	(1) Rosas et al. (1999)
	0.83[3]	0.07[5]	0.002[3]	0.0009[2]	(2) Stevens (1991)
	0.03[5]	0.46[7]	0.002[5]	0.00006[3]	(3) Staven et al. (2003)
	0.002[6]	0.002[13]	0.0024[10]	0.00018[4]	(4) Pérez-Carrera and Fernández-Cirelli (2005)
	0.00147[15]	0.000842[15]	0.0024[11]	0.0002[4]	(5) Technical Support Document (2012)
			0.00028[12]	0.000093[4]	(6) Hickox (2000)
			0.00136[7]	0.000052[4]	(7) Cornelis et al. (2016)
			0.0017[5]	0.000044[4]	(8) Beni et al. (2008)
			0.002[14]	0.00005[5]	(9) EPA (1998)
			0.002[15]	0.00071[5]	(10) Vreman et al. (1986)
				0.00057[2]	(11) Ham et al. (1949)
				0.000063[2]	(12) Bruce et al. (2003)
				0.000062[6]	(13) Bureau of Land Management (1997)
				0.00019[1]	(14) Secil (2007)
				0.0001[7]	(15) Durham and York Waste (2007)
				0.00022[1]	
				0.00016[1]	
				0.00014[1]	
				0.00067[1]	
				0.000368[8]	
				0.000555[8]	
				0.006[9]	
				0.000062[13]	
Transfer factor	Min 0.001 Max 0.83	Min 0.0008 Max 0.46	0.00085	1.46652E − 05	

Table 6a
Summary Table of Estimated Daily Intake (EDI) values of total arsenic due to consumption of livestock and livestock products.

EDI summary table	5th	Mean	95th	Units
Poultry	6.86×10^{-4}	1.30×10^{-2}	4.30×10^{-2}	$\mu g\, kg^{-1}$ bw day^{-1}
Eggs	2.62×10^{-4}	5.84×10^{-3}	1.96×10^{-2}	$\mu g\, kg^{-1}$ bw day^{-1}
Beef	2.75×10^{-2}	1.23×10^{-1}	2.89×10^{-1}	$\mu g\, kg^{-1}$ bw day^{-1}
Milk	4.40×10^{-3}	9.62×10^{-2}	3.35×10^{-1}	$\mu g\, kg^{-1}$ bw day^{-1}
Cumulative exposure		0.23789		$\mu g\, kg^{-1}$ bw day^{-1}

Table 6b
Summary Table of Estimated Daily Intake (EDI) values of inorganic arsenic due to consumption of livestock and livestock products.

EDI summary table	5th	Mean	95th	Units
Poultry	4.55×10^{-6}	1.29×10^{-4}	4.48×10^{-4}	$\mu g\, kg^{-1}$ bw day^{-1}
Eggs	1.93×10^{-6}	5.82×10^{-5}	2.16×10^{-4}	$\mu g\, kg^{-1}$ bw day^{-1}
Beef	1.73×10^{-4}	1.22×10^{-3}	3.51×10^{-3}	$\mu g\, kg^{-1}$ bw day^{-1}
Milk	3.05×10^{-5}	9.32×10^{-4}	3.40×10^{-3}	$\mu g\, kg^{-1}$ bw day^{-1}
Cumulative exposure		0.00234		$\mu g\, kg^{-1}$ bw day^{-1}
Suggested BMDL		0.3–8.0		$\mu g\, kg^{-1}$ bw day^{-1}

A Provisional Tolerable Weekly Intake (PTWI) is often used to describe the endpoint of contaminants which have cumulative properties, such as As (Nabrzyski, 2006). In 1988, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an initial PTWI value of $15\,\mu g\, kg^{-1}$ bw $week^{-1}$ for As_{Inorg} (equivalent to $2.1\,\mu g\, kg^{-1}$ bw day^{-1}; WHO, 1988). This initial PTWI was withdrawn by JECFA in 2010, as it was deemed no longer appropriate. In its place, the JECFA proposed a Benchmark Dose Lower Confidence Limit ($BMDL_{01}$) of $3\,\mu g\, kg^{-1}$ bw day^{-1} with an associated range of $2.0–7.0\,\mu g\, kg^{-1}$ bw day^{-1}. This BMDL was put forward as the benchmark dose for As_{Inorg} for a 0.5% increase in cancer incidences of the lung, skin and bladder (JECFA, 2011). The European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM, 2009), which provides scientific advice on contaminants in the food chain, proposed a safe $BMDL_{01}$ level for As_{Inorg} of between 0.3 and $8.0\,\mu g\, kg^{-1}$ bw day^{-1} (EFSA, 2010).

Arsenosugars are thought to be less toxic than As(III) and As(V) (Yu et al., 2015), and possess "limited toxicity" (EFSA, 2005). Unlike terrestrial plants whose As species occur mainly as As_{Inorg} (particularly arsenite As(III) and arsenate As(V) (Quaghebeur and Rengel, 2005), marine phyta contain a much higher proportion of As_{Org} (as organosugars, in the form of arsenoribosides) (Jedynak et al., 2009). As such, it was recommended by JECFA to consider As species in seaweed differently to those found in terrestrial plants. Evidence to suggest a link between As_{Org} in food and the adverse human toxicological effect appears scarce (e.g. Woods, 1999; Trumbo et al., 2001; Uneyama et al., 2007; EFSA, 2010). JECFA has reported no ill health effects from populations who routinely consume high levels of As_{Org} directly from their diet ($> 50\,\mu g\, kg^{-1}$ bw day^{-1}). Considering this, a $BMDL_{01}$ has not been set for As_{Org}. Nevertheless, some caution should be taken as some As_{Org} species (i.e. monomethylarsonic) are thought to be a precursor of As_{Inorg} exposure through different demethylation processes (Feldmann et al., 2000). As such, arsenosugars should not be considered as having no potential for toxicity.

4. Results and discussion

4.1. Arsenic concentration in seaweed animal feed

Statistical analysis revealed higher levels of both As_{Tot} (t-value = 6.907; p-value < 0.001) and As_{Inorg} (t-value = 5.236; p-value < 0.001) in smaller grain size fractions of the SAF (Fig. 2). In the larger grain size (LG-SAF) the As_{Tot} concentrations ranged from $31.1–49.1\,\mu g\, g^{-1}$ for LG-SAF (mean $38.8\,\mu g\, g^{-1}$), while a concentration range of $33.8–56.3\,\mu g\, g^{-1}$ (mean $43.1\,\mu g\, g^{-1}$) was observed for SG-SAF (SI Sheet 3 Table S8). A similar trend was observed for As_{Inorg} concentrations with LG-SAF displaying an As_{Inorg} range of $0.1–1.3\,\mu g\, g^{-1}$ while for SG-SAF the range was $0.1–1.4\,\mu g\, g^{-1}$.

These results showed that As_{Inorg} is a minor constituent of the overall As_{Tot} in SAF which are in agreement with findings reported by the Biancarosa et al. (2017) and Morrison et al. (2014) who report the level of As_{Inorg} in feed grade *A. nodosum* to be in the range $0.1–2.4\,\mu g\, g^{-1}$ and $\sim 0.2\,\mu g\, g^{-1}$, respectively. Similarly, levels of As_{Tot} in this study ($31.1–56.3\,\mu g\, g^{-1}$) were in the range of values published by Biancarosa et al. (2017) (Phaeophyceae; $28–107\,\mu g\, g^{-1}$ dw) and

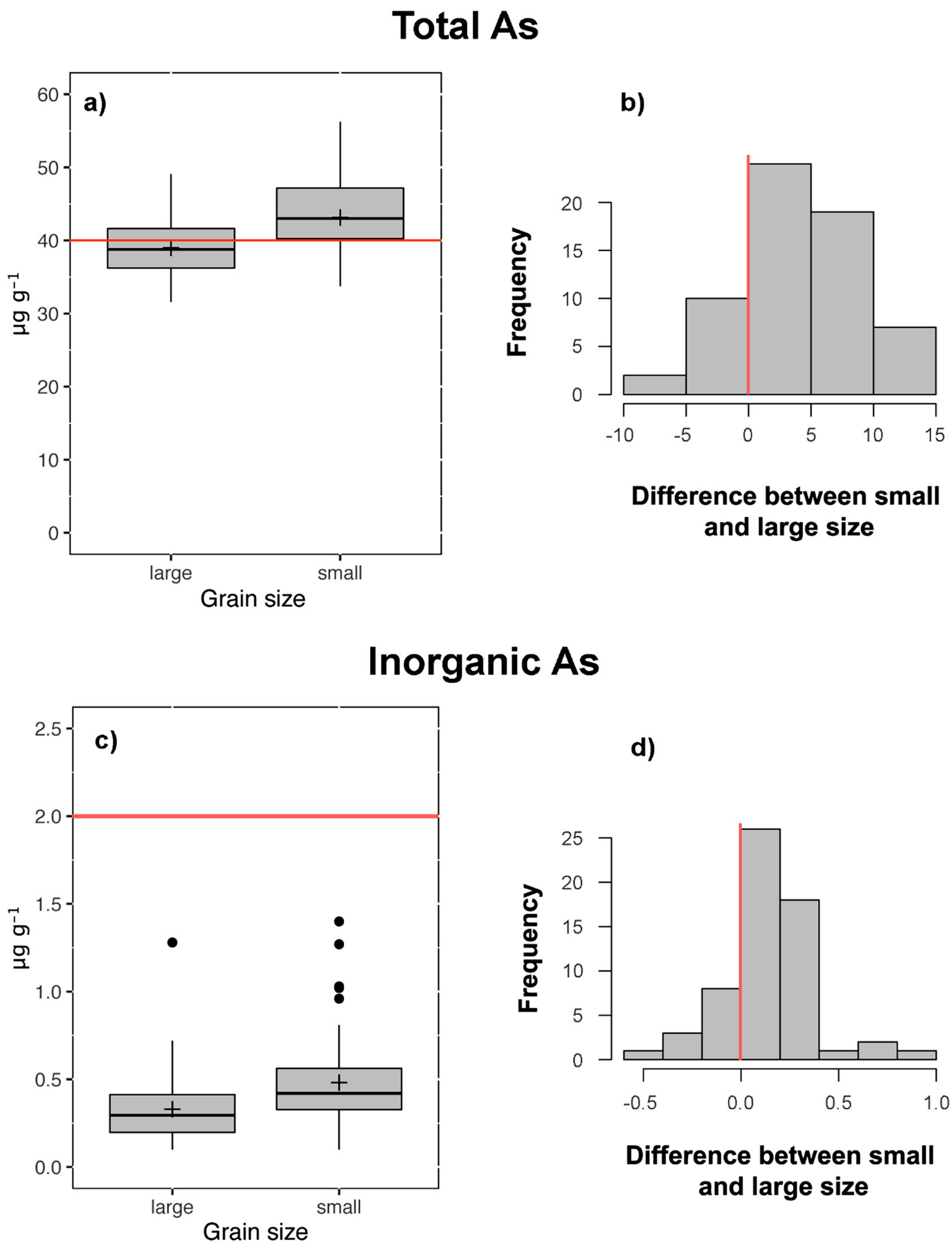

Fig. 2. Box plots for the total (a) (n = *124*) and inorganic (c) (n = *120*) arsenic concentrations according to grain size (n = X). Histograms showing the distribution of the difference between the small and large size for total (b) and inorganic (d) arsenic concentrations. Box plots indicate the median (bold line near the centre), the first and third quartile (the box), the mean (the cross), the extreme values whose distance from the box is at most 1.5 times the inter quartile range (whiskers), and remaining outliers (dark dots). Legal limits are indicated by a horizontal red line in box plot, and no differences (0) is indicated by a vertical red line in histograms. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Lunde (1970) and Morrison et al. (2014) (22–53.4 μg g^{-1}), for *A. nodosum* from Norway and Ireland.

The reasons for the higher As concentrations in the SG-SAF are not clear and may be related to a methodological bias. It is possible that the size of SG-SAF could improve the efficiency of metal extraction during the acid digestion stage of the sample processing due to the higher surface/volume ratio compared with the LG-SAF. Considering As_{Tot} concentrations are close to the European Limit of 40 μg g^{-1}, this could have important implications for SAF producers.

4.2. Livestock contribution to arsenic daily intake

Our results indicated that the concentration of As in livestock produce is low (SI Sheet 3 Table S7) and in general agrees with previous studies (see below). Once SAF is ingested by both poultry and cattle, As_{Inorg} is readily transported to the liver, spleen, kidneys, and lungs (Erry et al., 2005) before being translocated to keratin-rich endpoints such as nails, hair, and eggshells (Shen et al., 2013). Biotransformation of As_{Inorg} initially reduces As(V) to the more toxic As(III) species. Then

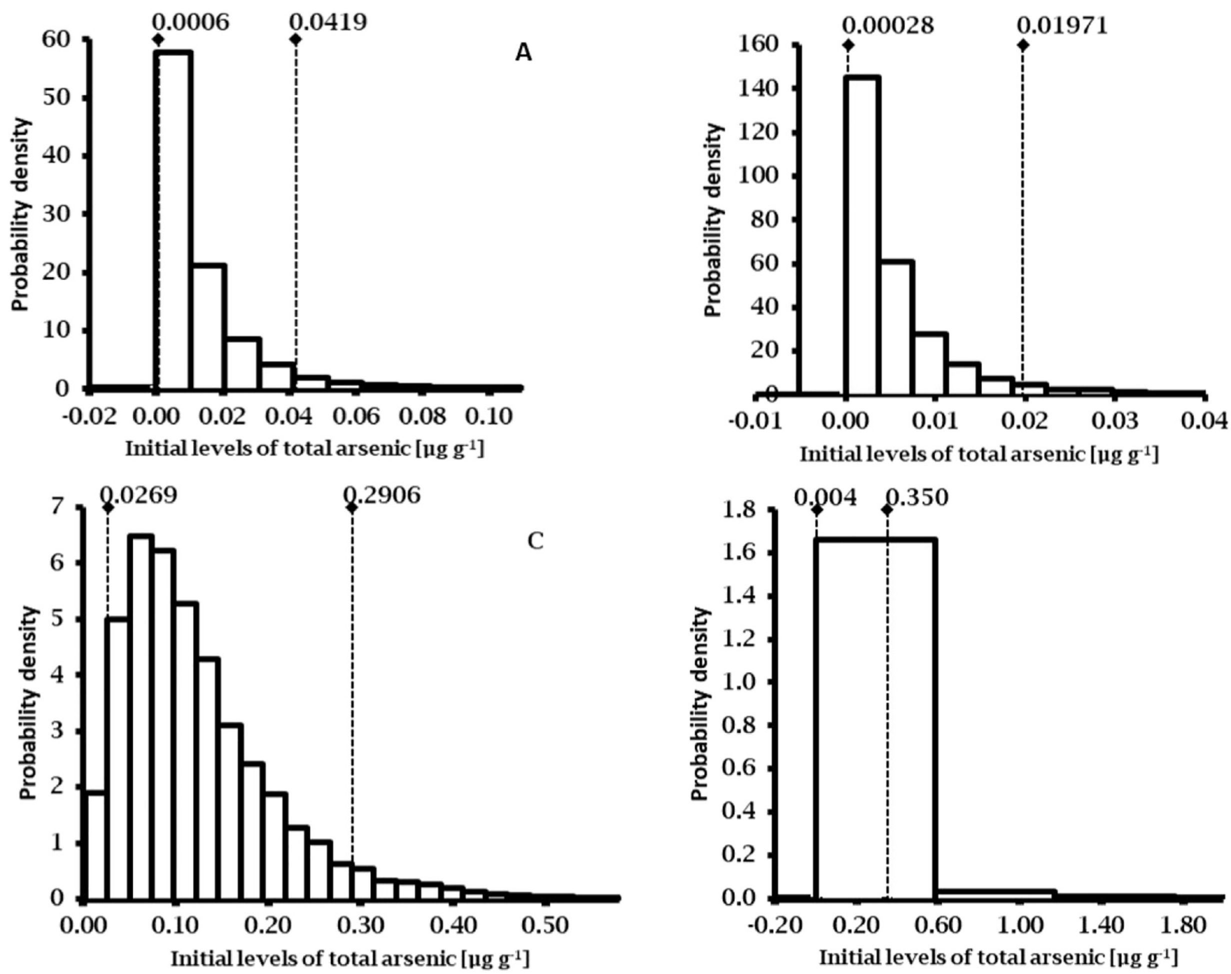

Fig. 3. Final exposure output of total arsenic ($\mu g\ g^{-1}$) to humans from A) poultry B) eggs C) beef and D) milk.

As_{Inorg} is enzymatically methylated to methyl arsenic (MA) and subsequently dimethyl arsenic (DMA) metabolites (Ventura-Lima et al., 2011). The As_{Inorg} is excreted primarily as these metabolites (Hughes et al., 2011). Although As_{Org} is considered much less toxic than As_{Inorg} species, methylated As_{Org} species such as DMA and MA show intermediate acute toxicity, being classed as Group 2B "possibly carcinogenic to humans" (evidence from animal studies) (Hedegaard and Sloth, 2011; Cullen and Reimer, 2016). Once *corporis*, these metabolites are excreted mainly in urine (Hopenhayn-Rich et al., 1993; Lopez-Alonso, 2012; Mendez et al., 2016). Species of As_{Org} are thought to be less extensively metabolised than As_{Inorg} and more rapidly excreted (Woods, 1999). This detoxification step and subsequent rapid excretion results in a very low carryover rate of As compounds from SAF into the edible tissue of poultry and cattle (EFSA, 2005).

Contrasting results were found by Feldmann et al. (2000) from seaweed-eating sheep of the Orkney Islands, which showed that appreciable concentrations of arsenosugars accumulated in the wool, blood, muscle, and kidneys. Bioaccumulation of As is a result of the differences between intake and excretion. In the case of intake, sheep from the Orkney Islands consumed ~4 kg of seaweed a day, mainly *Laminaria* spp., at a rate 40× higher than that of cattle in our study (~120 g). Moreover, the initial concentration of As_{Tot} in *Laminaria* is also > 2× that of *A. nodosum*. In the case of excretion, differences between poultry, cattle, and sheep are also expected. The known higher consumption rate of seaweed by sheep from the Feldmann et al. (2000) study, coupled with the unknown differences in excretion rates from sheep compared to cattle, may explain the results of the two studies. The authors of the present study wish to stress that it is important to follow producer guidelines regarding daily inclusion rates of SAF in livestock diets.

The cumulative EDI of As_{Tot} calculated in this study from consumption of poultry, eggs, beef, and milk was $0.2\ \mu g\ kg^{-1}$ bw day^{-1} (Table 6a), whereas the cumulative EDI for As_{Inorg} is $2.3 \times 10^{-3}\ \mu g\ kg^{-1}$ bw day^{-1} (Table 6b). The EDI calculated in this study for all livestock produced at the 95th percentile was < 0.01% of the $BMDL_{01}$ for As_{Inorg}. It was concluded that consumption of poultry, eggs, beef and milk from livestock products fed a diet containing SAF results in a low transfer of As to humans, well below the considered safe limit suggested by CONTAM (EFSA, 2010).

To date, few studies have directly quantified the potential for As transfer in humans as a result of intake of products from livestock fed diets containing seaweed meal. Although the risks to human health due to the consumption of contaminated livestock is yet to be fully understood, this study has shown that the potential for transfer of As into the meat of livestock and the produce of these animals is extremely low. The range of intakes calculated in this study is well below the $BMDL_{01}$ range suggested by both JECFA and CONTAM. It should be noted, however, that humans may be routinely exposed to As from a number of environmental sources, both natural and anthropogenic, and may be ingested in a number of ways. These environmental sources may contribute to the cumulative load of As in human diets and should be considered when estimating total As dietary intake by humans.

4.2.1. Chicken and eggs

As a result of chicken consumption As_{Tot} intake distribution was in the range of $0.00–0.04\ \mu g\ kg^{-1}$ bw day^{-1} (90% confidence) with a mean EDI of $0.01\ \mu g\ kg^{-1}$ bw day^{-1} (Fig. 3a). The resulting As_{Inorg}

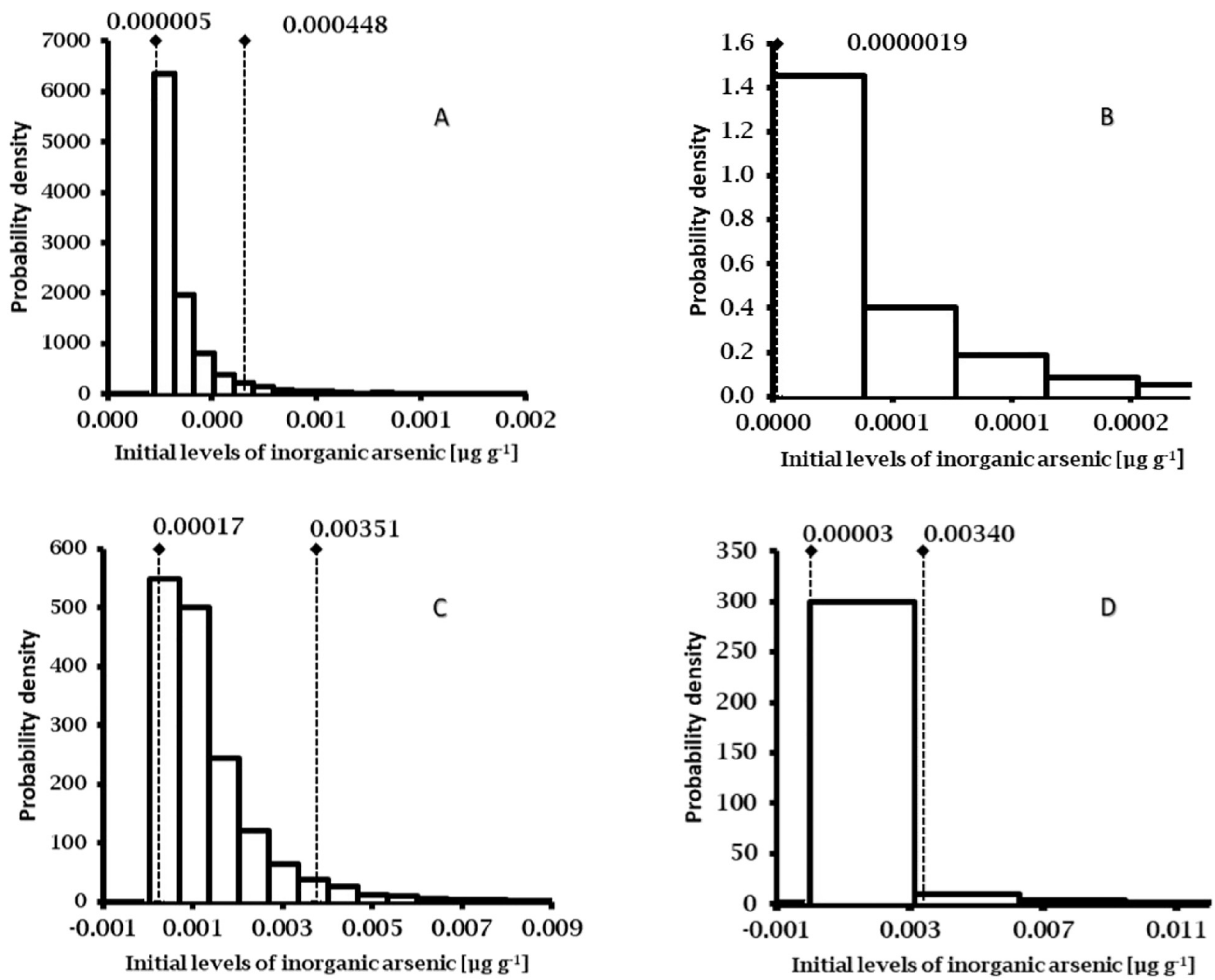

Fig. 4. Final exposure output of inorganic arsenic (μg g^{-1}) to humans from A) poultry B) eggs C) beef and D) milk.

intake distribution was in the range 0.00–4 × 10^{-4} μg kg^{-1} bw day^{-1} (90% confidence) with a mean EDI of 1 × 10^{-4} μg kg^{-1} bw day^{-1} (Fig. 4a).

As a result of egg consumption As_{Tot} intake distribution was in the range 0.00–2 × 10^{-4} μg kg^{-1} bw day^{-1} (90% confidence) with a mean EDI of 0.01 μg kg^{-1} bw day^{-1} (Fig. 3b). The resulting As_{Inorg} intake distribution was in the range 0.00–2 × 10^{-4} μg kg^{-1} bw day^{-1} (90% confidence) with a mean EDI of 1 × 10^{-4} μg kg^{-1} bw day^{-1} (Fig. 4b), equating to 0.003–0.005% of the JECFA and EFSA proposed BMDL for As_{Inorg}.

Important differences were found in the EDI and As concentration in chicken meat when compared with previous studies (FDA, 1993; Lasky et al., 2004). The obtained EDI for chicken in the present study was much lower than reported As intakes from previous studies (conducted prior to the international prohibition of arsenic-based feed additives, such as roxarsone) using similar consumption rates (0.02–0.07 μg kg^{-1} bw day^{-1} for As_{Tot} and 0.08–0.12 μg kg^{-1} bw day^{-1} for As_{Inorg}, based on a body weight of 70 kg; Lasky et al., 2004). This additive was recently prohibited in many countries (2013–2016), including the EU and North America (Hu et al., 2017) which may explain these differences. Results from the current study suggested that SAF does not contribute appreciably to the final As concentration in chicken meat, since As concentration is 0.00015 μg g^{-1}, three orders of magnitude lower than that previously reported by Lasky et al. (2004). Dorne and Fink-Gremmels (2012) have stated that as a result of pre-systemic and systemic eliminations the concentration of As that remains present in poultry tissue and eggs is much lower than the original concentration in SAF.

Our results agree with previous studies which state that the biological transmission of As into the meat and produce of poultry and eggs is unlikely to be high, and foodstuffs from these animals are unlikely to contribute appreciably to any form of human harm (Khalafalla et al., 2011; Ghosh et al., 2012; Mandal, 2017).

4.2.2. Beef and milk

Due to the high consumption rates of bovine livestock coupled with cattle's own high dietary requirements, highest EDIs for As_{Tot} and As_{Inorg} are found in beef. The intake distribution of As_{Tot} was in the range 0.03–0.29 μg kg^{-1} bw day^{-1} (90% confidence) with a mean EDI of 0.1 μg kg^{-1} bw day^{-1} (Fig. 3c). In the case of As_{Inorg} intake, the distribution ranged between 0.00 and 3.5 × 10^{-3} μg kg^{-1} bw day^{-1} (90% confidence) with a mean EDI of 1.2 × 10^{-3} μg kg^{-1} bw day^{-1} (Fig. 4c). Consequently, this results in an approximate intake 0.04–0.06% of the proposed $BMDL_{01}$ for As_{Inorg} (EFSA, 2010; JECFA, 2011). The resulting distribution model used for milk produced an EDI range of As_{Tot} 0.00–0.35 μg kg^{-1} bw day^{-1} (90% confidence) with a mean EDI of 0.1 μg kg^{-1} bw day^{-1} (Fig. 3d). The calculated As_{Inorg} intake distribution was in the range 0.0–3.4 × 10^{-3} μg kg^{-1} bw day^{-1} (90% confidence) with a mean EDI of 9 × 10^{-4} μg kg^{-1} bw day^{-1} (Fig. 4d).

Numerous studies have previously examined the transfer of As into dairy milk and beef obtaining similar As concentrations to those found in the present study (Vreman et al., 1986; Crout et al., 2004; Pérez-Carrera and Fernández-Cirelli, 2005). According to Lopez Alonso et al. (2000), As concentrations in beef in some European and North

American countries are in the same order of magnitude as those reported here (average range 0.004–0.02 μg g^{-1}; our study 0.002 μg g^{-1}). In the case of milk, Cervera et al. (1994) calculated the As the content of milk to be 0.0001–0.0008 μg g^{-1}, also in agreement with the findings of the present study (0.00035 μg g^{-1}; SI Sheet 3 Table S7). These results suggest that the transfer of As from SAF to milk and beef are negligible and do not contribute substantially to the daily As_{Inorg} BMDL of 3 μg kg^{-1} bw day^{-1} (JECFA, 2011), highlighted by a low EDI (Table 6b). In this sense, our results of human exposure to As (i.e. EDI) reinforce the idea that "food derived from terrestrial animals contributes only insignificantly to human exposure, due mainly to the low transfer rate of As_{Inorg} to edible tissue of mammals and poultry" as stated by the European Food Safety Authority (EFSA, 2005).

5. Conclusions

Over the 5-year study, both As_{Tot} and As_{Inorg} concentrations were predominately significantly higher in the finer grade *A. nodosum* animal feed. In addition, As_{Tot} levels from finer grade *A. nodosum* animal feed were also predominately at or above the limit of 40 μg g^{-1} set under EC Regulation 2015/186 (EU, 2015). In general, As_{Tot} concentrations in the larger grade material were below the regulated limit (< 40 μg g^{-1}). The concentrations of As_{Inorg} in the *A. nodosum* animal feed over the duration of the study never exceeded the EC Regulation limit of 2 μg g^{-1}, an important finding considering the greater toxicity of As_{Inorg}. Arsenic toxicity is species specific, and therefore speciation analysis is critical when assessing the feed to food transfer and potential human exposure to arsenic from SAF. Oral ingestion of food and feed is one of the primary routes for As_{Inorg} entry into mammalian and poultry systems. The current study found EDI levels to be within the adequate range set by EFSA and JECFA for the safe use of *A. nodosum* as a raw ingredient in the diets of animals reared for human consumption. This study indicated that the EDI of As as a result of the consumption of livestock fed *A. nodosum* animal feed is negligible. When compared with the established $BMDL_{01}$ of 3 μg kg^{-1} bw day^{-1} ^{for} As_{Inorg}, all exposure outputs (chicken, eggs, beef, and milk) fell below exposure values calculated at the 95th percentile, and it can be concluded that As transfer does not constitute a hazard to human health. The EDI calculated in this study, however, should be considered alongside other human dietary intakes of As which follow consumption of a fully balanced diet. Results from this study should be thought of as part of a cumulative intake effort of As in our diet. Consequently, a total diet exposure assessment would be relevant. It should be noted that the models used in this study are applicable only to scenarios considered. Should new knowledge emerge, specifically regarding toxicity endpoints or biotransfer rates, the assessment should be reevaluated.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.05.032.

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