

Low inorganic arsenic in hydrolysed-rice formula used for cow's milk protein allergy

Meyer, R., Carey, M. P., Turner, P., & Meharg, A. A. (2018). Low inorganic arsenic in hydrolysed-rice formula used for cow's milk protein allergy. *Pediatric allergy and immunology* : official publication of the European Society of Pediatric Allergy and Immunology. Advance online publication. https://doi.org/10.1111/pai.12913

Published in:

Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology

Document Version: Peer reviewed version

Queen's University Belfast - Research Portal:

Link to publication record in Queen's University Belfast Research Portal

Publisher rights © 2018 EAACI and John Wiley and Sons A/S. This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access

This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. - Share your feedback with us: http://go.qub.ac.uk/oa-feedback

Article type : Letter to the Editor

Title: Low inorganic arsenic in hydrolysed-rice formula used for cow's milk protein allergy

To the Editor

Hypoallergenic formulas are recommended for use in young children with cow's milk protein allergy (CMPA), where breastmilk is not available,¹ with the choice between both extensively hydrolysed casein/whey or amino acid-based products. More recently, hydrolysed rice protein-based formulas (HRF) have become available and are now commonly used in Europe for CMPA. Some of these formulas have gone through the clinical trials required for hypoallergenicity according to EAACI guidelines and have shown their suitability for children with CMPA.^{2, 3} However, concerns have been raised with respect to the arsenic content in infant rice products.^{4, 5}

Arsenic is a ubiquitous metalloid present at low concentrations in rocks, soil and natural ground water, mainly in inorganic forms.⁶ The International Agency for Research on Cancer classifies inorganic arsenic [As(V)] as carcinogenic to humans, and concerns have been raised with respect to exposure, particular in early childhood (where relative exposure is greater due to smaller body mass). A publication from the USA in 2012 found that non-dairy based infant formulas had significantly more As(V) than cow's milk-based equivalents.⁷ HRF are gaining popularity, due to both palatability and cost. We therefore sought to assess levels of arsenic in commonly-used HRF in Europe.

For this study HRF were sourced from Italy, France and Belgium and analysed at the Institute for Global Food Security, Queen's University Belfast. For each brand, we analysed samples taken from two different batch numbers, testing 2 samples (from separate tins) for each batch. We used the method of Meharg et al.⁴ for analysis. In brief, 100 mg of each sample was microwave-digested at 95°C in 10 ml of 1% nitric acid. A certified reference material (CRM), rice flour NIST1568b, was used for quality control in each analytical batch [variance 2.1% for AS(V)]. Samples, blanks and CRMs were tested in triplicate for arsenic content using Ion Chromatography-Inductively Coupled Plasma Mass Spectrometry (ThermoScientific iCap Q ICP-MS coupled to Thermo IC5000 Ion Chromatograph) with a gradient mobile phase for separation of all arsenic species. The results of the analysis are shown in Table 1.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12913

We analysed dry formula powder rather than reconstituted formula, to eliminate confounding due to arsenic present in household water. Levels of inorganic arsenic in all the HRF samples tested were very low, and similar to that reported by Vela et al. for conventional cow's milk infant formula ⁸ but slightly higher than that reported by Jackson et al. using a different analysis platform.⁷ The average volume of consumption of hypoallergenic formula at 0-6 months is 600-800 ml per day, which would require 90-120g of powder (based on an average scoop size of 4.5g for HRF). This would equate to 1.3-1.8 µg of As(V), which in an 8 kg infant (50th centile for weight, z score 0) is an exposure of 0.16-0.23 µg/kg body weight (b.w.). This is well below the average exposure in childhood generated from data produced by European Food Safety Authority (EFSA) for both infants [0.24 ug/kg - 0.43 ug/kg b.w./per day] and toddlers [0.32-0.45 ug/kg per b.w./day].⁶ The As(V) exposure based on an average infant would also be 10-fold less than the limit for exposure set by the World Health Organisation at 2ug/kg per b.w./day. It is important to note that all these studies are based on analysis of formula powder; actual As(V) exposure is significantly influenced by the arsenic in the tap water used to reconstitute the formula, which (according to EFSA) is 1.1-2.0 µg/kg b.w. There is no maximum level set by EFSA for infant formulas currently, but water for human consumption is set at 10 ug/L (Council Directive 98/83/EC).

Table 1: Summary of hydrolysed	l rice formulas analysed in	n this study and results	of arsenic content
--------------------------------	-----------------------------	--------------------------	--------------------

Name of feed	Origin	Characteristic	As(V)* (ug/kg)	DMA ◊ (ug/kg)	Sum of Species [As(V)+DMA] (ug/kg)
Modilac Expert Riz 1(batch one)	France	Hydrolysed rice suitable from 0- 6 months	9	2	11
Modilac Expert Riz 1 (batch 2)	France	Hydrolysed rice suitable from 0- 6 months	20	15	35
Modilac Expert Riz 2 (batch 1)	France	Hydrolysed rice suitable from 6- 12 months	12	13	25
Modilac Expert Riz 2 (batch 2)	France	Hydrolysed rice suitable from 6- 12 months	13	14	27
Modilac Expert Riz AR 1 (batch 1)	France	Hydrolysed rice suitable from 0- 6 months thickened with carob and corn starch	14	19	33

France	Hydrolysed rice	12	6	18
	suitable from 6-			
	12 months			
	thickened with			
	carob and corn			
	starch			
Belgium and	Extensively	11	3	13
France	hydrolysed rice			
	from 0-12			
	months			
Belgium and	Extensively	11	3	13
France	hydrolysed rice			
	from 0-12			
	months			
Italy	Hydrolysed rice	9	6	15
	suitable from 0-			
	12 months			
Italy	Hydrolysed rice	10	5	15
	suitable from 0-			
	12 months			
	France Belgium and France Belgium and France Italy	FranceHydrolysed ricesuitable from 6-12 monthsthickened withcarob and cornstarchBelgium andExtensivelyFrancehydrolysed ricefrom 0-12monthsBelgium andExtensivelyFrancehydrolysed ricefrom 0-12monthsItalyHydrolysed riceItalyHydrolysed riceItalyHydrolysed ricesuitable from 0-12 months	FranceHydrolysed rice suitable from 6- 12 months thickened with carob and corn starch12Belgium and FranceExtensively hydrolysed rice from 0-12 months11Belgium and FranceExtensively hydrolysed rice from 0-12 months11Belgium and LabelExtensively from 0-12 	FranceHydrolysed rice suitable from 6- 12 months thickened with carob and corn starch126Belgium and FranceExtensively hydrolysed rice from 0-12 months113Belgium and FranceExtensively hydrolysed rice from 0-12 months113Belgium and FranceExtensively hydrolysed rice from 0-12 months113Belgium and FranceExtensively hydrolysed rice from 0-12 months113Belgium and FranceExtensively hydrolysed rice from 0-12 months113ItalyHydrolysed rice suitable from 0- 12 months96ItalyHydrolysed rice suitable from 0- 12 months105

◊DMA = dimethylarsinic acid

The limit of detection (LOD) for all species by HPLC-ICP-MS (calculated from DMA calibration) were 0.0003 mg/kg.

The main limitation of this study was that samples were not compared to extensively hydrolysed or amino acid formula, which are the mainstay of treatment formulas for CMPA. However, the latter have been used for the last 60 years in the treatment of CMPA and were assumed safe. In the light of current data, a future study establishing As(V) levels also in these formulas would be recommended.

In conclusion, this study found that As(V) levels in hydrolysed rice formulas are well within the safe range as stipulated by EFSA/WHO. However, it is important take the source of water into account when mixing formulas, which may affect levels.

References

- 1. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014;69:1008-1025.
- Vandenplas Y, De GE, Hauser B. An extensively hydrolysed rice protein-based formula in the management of infants with cow's milk protein allergy: preliminary results after 1 month. Arch.Dis.Child 2014;99:933-936.
- Vandenplas Y, De GE, Hauser B. Safety and tolerance of a new extensively hydrolyzed rice protein-based formula in the management of infants with cow's milk protein allergy. Eur J Pediatr 2014;173:1209-1216.
- 4. Meharg AA, Deacon C, Campbell RC, et al. Inorganic arsenic levels in rice milk exceed EU and US drinking water standards. J Environ.Monit. 2008;10:428-431.
- 5. Signes-Pastor AJ, Carey M, Meharg AA. Inorganic arsenic in rice-based products for infants and young children. Food Chem 2016;191:128-34.
- 6. European Food Safety A. Dietary exposure to inorganic arsenic in the European population. EFSA Journal 2014;12:63.
- 7. Jackson BP, Taylor VF, Punshon T, et al. Arsenic concentration and speciation in infant formulas and first foods. Pure Appl Chem 2012;84:215-223.
- Vela NP, Heidkemper DT. Total arsenic determination and speciation in infant food products by ion chromatography-inductively coupled plasma-mass spectrometry. J AOAC Int. 2004;81:244-252.

Authors

Rosan Meyer, Imperial College, London W2 1NY, UK and corresponding author – r.meyer@imperial.ac.uk

Manus P Carey, Institute for Global Food Security, Queen's University Belfast, David Keir Bld, Malone Rd, Belfast, BT5 5BN, Northern Ireland

Paul Turner, Imperial College, London W2 1NY, UK

Andrew. A. Meharg, Institute for Global Food Security, Queen's University Belfast, David Keir Bld, Malone Rd, Belfast, BT5 5BN, Northern Ireland

Contribution of Authors

RM write up of manuscript and sourcing of rice formulas in Europe used for cow's milk protein allergy

MC laboratory analysis and review of manuscript

PT critical review of manuscript

AM critical review of manuscript and direction of methodology of the study

Conflict of Interest

None of the authors declare any conflict of interest pertaining the current publication

Source of funding

No funding was required for this study