Revista Visa em debate sociedade, ciência & tecnologia

REVIEW
https://doi.org/10.3395/2317-269x.00789

Honey health risk in Brazil related to new threats: emerging chemical residues and contaminants

Risco sanitário do mel no Brasil em relação a novas ameaças: resíduos e contaminantes químicos emergentes

Thiago Bousquet Bandini[I,*]

Bernardete Ferraz Spisso[II]

[I] Instituto de Tecnologia em Fármacos, Fundação Oswaldo Cruz (Far-Manguinhos/Fiocruz), Rio de Janeiro, RJ, Brasil

[II] Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz (INCQS/Fiocruz), Rio de Janeiro, RJ, Brasil

* **E-mail:** thiago.farmanguinhos@gmail.com

Received: May 31, 2016
Approved: Feb 06 2017

ABSTRACT

This narrative literature review deals with the honey, its context as a product of varied uses and with significant socio-economic relevance, aiming to describe some emerging chemical residues and contaminants and their aspects related to Health Surveillance. Honey is a substance that, beyond being used as food since the beginning of human civilization, also has therapeutic and pharmacothecnical applications. Brazil is among the major world producers and exporters of honey and this production play a relevant socio-economic role in the country. Like other products of animal origin, honey is subject to the presence of residues of substances used in the protection of swarms and contaminants from the environment. Despite the presence of substances in honey with potential impact on health is expected by health agencies, it is required to update as to which substances should or should not be monitored. This review lists examples of classes of substances that are not currently monitored, considered as “emerging” for not being regulated properly in Brazil and in many parts of the world. For the emerging contaminants covered here, scientific publications with national data are scarce or non-existent when it comes to honey, showing that new scientific knowledge production is needed in this area. It is recommended further study of the occurrence of quinolones, pyrrolizidine alkaloids, grayanotoxins and substances used in the production of polymers in honey in Brazil, so that health risks from the consumption of honey containing these substances are known and minimized or eliminated.

KEYWORDS: Honey; Residues; Contaminants; Fitotoxins; Quinolones; Sanitary Surveillance

RESUMO

Esta revisão de literatura narrativa trata do mel, sua contextualização como produto de variadas utilizações e com significativa relevância socioeconômica, tendo como objetivo descrever alguns resíduos e contaminantes químicos emergentes e seus aspectos relacionados à Vigilância Sanitária. O mel é uma substância que, além de ser utilizada como alimento desde o início da civilização humana, possui aplicações terapêuticas e farmacotécnicas. O Brasil está entre os grandes produtores e exportadores mundiais de mel, cuja produção tem relevante papel socioeconômico no país. Como outros produtos de origem animal, o mel está sujeito à presença de resíduos de substâncias utilizadas na proteção dos enxames e de contaminantes provenientes do meio ambiente. Apesar da presença de substâncias no mel com potencial impacto na saúde ser esperada pelas agências sanitárias, é necessária a atualização quanto a quais substâncias devem ou não ser monitoradas. Essa revisão relaciona exemplos de classes de substâncias que atualmente não são monitoradas, tidas como “emergentes” por ainda não serem regulamentadas adequadamente no Brasil e em diversas partes do mundo. Para os contaminantes emergentes aqui tratados, publicações científicas com dados nacionais são escassas ou inexistentes quando se trata de mel, demostrando que há necessidade de produção de conhecimento científico nessa área. Recomenda-se mais estudos acerca da ocorrência de quinolonas, alcaloides pirrolizidínicos, graianotoxinas e de substâncias utilizadas na produção de polímeros em mel no Brasil, para que riscos sanitários provenientes do consumo de mel contendo essas substâncias possam ser conhecidos e minimizados ou eliminados.

PALAVRAS-CHAVE: Mel; Resíduos; Contaminantes; Fitotoxinas; Quinolonas; Vigilância Sanitária

INTRODUCTION

This paper literature review addresses some emerging chemical residues and contaminants in honey.

Definitions about honey, its uses in different areas, and its socio-economic relevance are brought into context within Brazil. The concepts of residues and contaminants in the production of honey are presented, and emerging residues and contaminants are considered extremely relevant, given the comparison of the state of the industry currently found in Brazil and abroad. The objective of this work is to analyze the scenarios of the Sanitary Surveillance department of the Brazilian National Health Surveillance Agency (VISA) for honey inside and outside the country, portraying the current situation of this animal product in relation to emerging contaminants.

METHOD

Literature reviews are extensive publications used to describe and discuss the development or the state-of-the-art of a given subject, from a theoretical or contextual point of view, playing a key role in continuing education[1].

Since this is a narrative literature review, we have gathered different bibliographical references, ranging from legislation to scientific articles in order to justify the relevance of honey, as well as discuss the VISA issues on the presence of residues and contaminants.

The references used in this work were selected randomly, but in such a way that we could draw a general overview on the subjects addressed throughout the text, focusing on the residues and contaminants discussed. These references are located in scientific databases such as *Science Direct*, *Scopus*, *Web of Knowledge*, SciELO, among others, for research studies using the keywords "*honey*" and "*contaminants*." From the results obtained, we evaluated articles that addressed contaminants not provided for or little discussed in either national or international laws or codes. The other references (legislation, codes, standards, analytical methodologies, other scientific articles) were researched directly to complement the discussion, whenever necessary. The search for references was carried out continuously between February 2014 and February 2017, and there was no limitation to the publication date for the selection of references.

DEFINITIONS AND USES OF HONEY

There are several definitions for honey, many of them complementary to each other, and it is interesting to highlight some of them. Honey as food can be described as:

> [...] a food product produced by honeybees, from the nectar of flowers or secretions from live parts of plants or excretions of plant-sucking insects on live parts of plants, which the bees collect, transform, combine with specific substances, store, and allow to mature in honeycombs.[2]

Another definition presents honey as "the viscous, aromatic, and sugary substance obtained from the nectar of flowers and or saccharine exudates that honeybees produce"[3]. This definition is similar to that used in VISA, which describes honey simply as the "natural product made by bees from flower nectar and or plant saccharine exudates"[4]. In pharmacognosy terms, honey is a substance that can be defined as:

> [...] a natural product supplied by the bee *Apis mellifera L.*, Apidae, comprising a concentrated aqueous solution of sugars, predominantly fructose and glucose, as well as small amounts of dextrins, enzymes, waxes, volatile oils, organic acids, ethers, gummy substances, albumin, and minerals[5].

Honey has been used by man as food since prehistory, preyed upon and exploited, causing environmental damage and death to the supplier of the product, the honeybees. Over time, however, man has developed ways to manage bees and honey production, which led to the development of beekeeping[3].

The use of honey as food is widespread, as it can be consumed pure or as an ingredient in many other types of food, industrialized or not. It can be found in bakery products, confectionery, breakfast cereals, marmalades and jams, dairy products, ice cream, and soft drinks; moreover, in many cultures, it was, and still is, an important source of fermentable sugars[6].

In addition to its use as food, or even as an ingredient for other types of food, honey has also been used in therapy, thanks to some of its properties, such as vitamins and minerals (Table). Many articles address these therapeutic applications[7-11].

Although there is not always consensus on some of honey's applications or therapeutic properties, several of its physiological effects have been scientifically proven and accepted by the *Food and Agriculture Organization of the United Nations*. These effects are[6]:

- Source of energy: it is a source of immediately-available calories, consisting mainly of the simple sugars fructose and glucose, which do not require complex processes for their digestion;
- Presence of non-energy nutrients: despite their low amount, the high quality and availability of micronutrients in raw honey are considered responsible for some physiological effects;
- Repair action in topical applications: under controlled conditions, honey accelerates regeneration in various types of injuries, from burns to postoperative healing, showing an effect that is superior to the application of purified sucrose and special preparations of powder polysaccharides, as well as preventing bandages and dressings sticking to the wound and to the new fragile layers of tissue that are formed;
- Antibacterial activity: this is the most easily-verifiable and most-studied property. Antibacterial activity occurs because of the high concentration of sugars and acidity (pH between 3.5 and 5.0) in raw honey and the presence of hydrogen peroxide in diluted honey. Hydrogen peroxide is an enzymatic byproduct obtained during the formation of glucuronic acid from glucose, and the enzyme responsible, glucose oxidase, remains inactive in honey at normal concentration[12].

Table. Nutrients in honey in relation to human need.

Nutrient	Unit	Average amount in 100 g of honey	Recommended daily intake
Energy equivalent	kcal	304	2,800
Vitamins			
A	I.U.	-	5,000
B1 (Thiamine)	mg	0.004-0.006	1.5
B2 (Riboflavin)	mg	0.002-0.060	1.7
Nicotinic Acid (Niacin)	mg	0.110-0.360	20
B6 (Pyridoxine)	mg	0.008-0.320	2
Pantothenic Acid	mg	0.020-0.110	10
Folic Acid	mg	-	0.4
B12 (Cyanocobalamin)	mg	-	6
C (Ascorbic Acid)	µg	2.2-2.4	60
D	mg	-	400
E (Tocopherol)	I.U.	-	30
H (Biotin)	I.U.	-	0.3
Minerals			
Calcium	mg	4-30	1,000
Chlorine	mg	2-20	-
Copper	mg	0.01-0.1	2
Iodine	mg	-	0.15
Iron	mg	1-3.4	18
Magnesium	mg	0.7-13	400
Phosphorus	mg	2-60	1,000
Potassium	mg	10-470	-
Sodium	mg	0.6-40	-
Zinc	mg	0.2-0.5	15

Source: Adapted from Krell[6].

Evidence of the effects listed above led to the approval of honey for medical use in the treatment of injuries in Australia in 1999, and dressings impregnated with honey for medical use in the United Kingdom in 2004. Currently, there are several commercial products available in Europe, Australia, Canada, and the United States, and the latter has the approval of the Food and Drug Administration[13,14]. In Brazil, information on honey with therapeutic uses was found, but without specific references to its specifications. These specifications appear to follow the United States pharmacopoeia[15].

Honey is also used in cosmetic formulations because its physicochemical properties allow it to perform pharmacotechnical functions, acting as an emollient, humectant, pH regulator and, to a degree, as an antimicrobial preservative[8], as well as being used as a vehicle[16].

SOCIOECONOMIC RELEVANCE OF HONEY IN BRAZIL

Brazil is one of the world's largest producers, and among the largest exporters, of honey. Until 2005, it was the 15th largest producer, and until 2007 stood out as the country that had most expanded its exports, both in amount and value. Until 2003, it was the seventh largest exporter[17]. In 2010, the country was 11th among world producers, and fifth largest exporter[18]. In 2013, there was a further increase in exports, reaching more than 16,000 metric tons, making Brazil the seventh largest exporter[19]. In 2014, an increase of 82% from 2013 in exports, took Brazil to the eighth position among the largest exporters, with just over 25,300 metric tons[20]. Despite the good performance in exports, the country held a better position in the world *ranking* in quantity rather than in value, indicating that smaller producers do not obtain better prices. This points to the need to improve the quality and added value of the product.

Figure 1 shows the consolidated data provided by the Brazilian Institute of Geography and Statistics, from the Automatic Recovery System[21], and the Department of Foreign Trade, from the *AliceWeb*[22] system, all in relation to natural honey, which is the only category available. The latter source indicates small volumes of honey imports between 2003 and 2007, with 2004 as the year with the largest import volume, of approximately 38 metric tons. After 2008, there are no records of honey import. No data were found that distinguished the different types of honey, either in this source or in others.

From the data presented, we can verify that Brazil is self-sufficient in relation to honey and is a relevant exporter. Therefore, production must comply with domestic and international sanitary requirements to avoid technical barriers and, more importantly, to avoid putting at risk both Brazilian consumers and consumers in the countries that import the country's honey.

The production of honey occurs throughout the country, and, in addition to extractivism, there is also beekeeping for the purpose of commercial exploitation. In addition to the native swarms and "artisanal" apiaries, there has also been the expansion of specialized production and beekeeping support activities[17]. In 2006, the Brazilian Service for Support of Micro and Small Enterprises estimated that 350,000 people lived in Brazil because of beekeeping, with significant representation of family agriculture in this area[23].

RESIDUES AND CHEMICAL CONTAMINANTS IN HONEY

Ensuring the safety of food is essential for the protection of human health. Honey, like many other animal products, is subject to chemical hazards both from the presence of residues of substances used to protect swarms and contaminants from the environment, such as pesticides, other organic contaminants (e.g. polychlorinated biphenyls), and inorganic contaminants (metals).

Despite the presence of substances in honey with potential impact on health being expected by health agencies, constant updating is needed as to which substances should or should not be monitored. In the following paragraphs, we present residues and contaminants usually expected by sanitary agencies, and we show examples of classes of relevant substances related to honey that are currently not monitored or even discussed in Brazil, such as waste and contaminants considered as "emerging" because they are not adequately regulated in Brazil or in various parts of the world.

Bogdanov[24] has classified the residues and contaminants found in bee products, which are shown in Figure 2.

Impurities that can occur in honey from the environment and that can be introduced into the hive by bees, are highlighted as follows:

- Inorganic pollutants such as lead from the burning of motor fuels (decreasing) and cadmium from the steel industry and catalysts, as well as plants absorbing cadmium from the ground;
- Organic pollutants such as polychlorinated biphenyls used as electrical insulating liquids (askarel) and polyaromatic compounds that have been used in the past and are still present in the environment;
- Agrochemicals, such as insecticides (organochlorines, organophosphates, carbamates, etc.), antimicrobials, fungicides, and, with relatively lower incidence, herbicides.

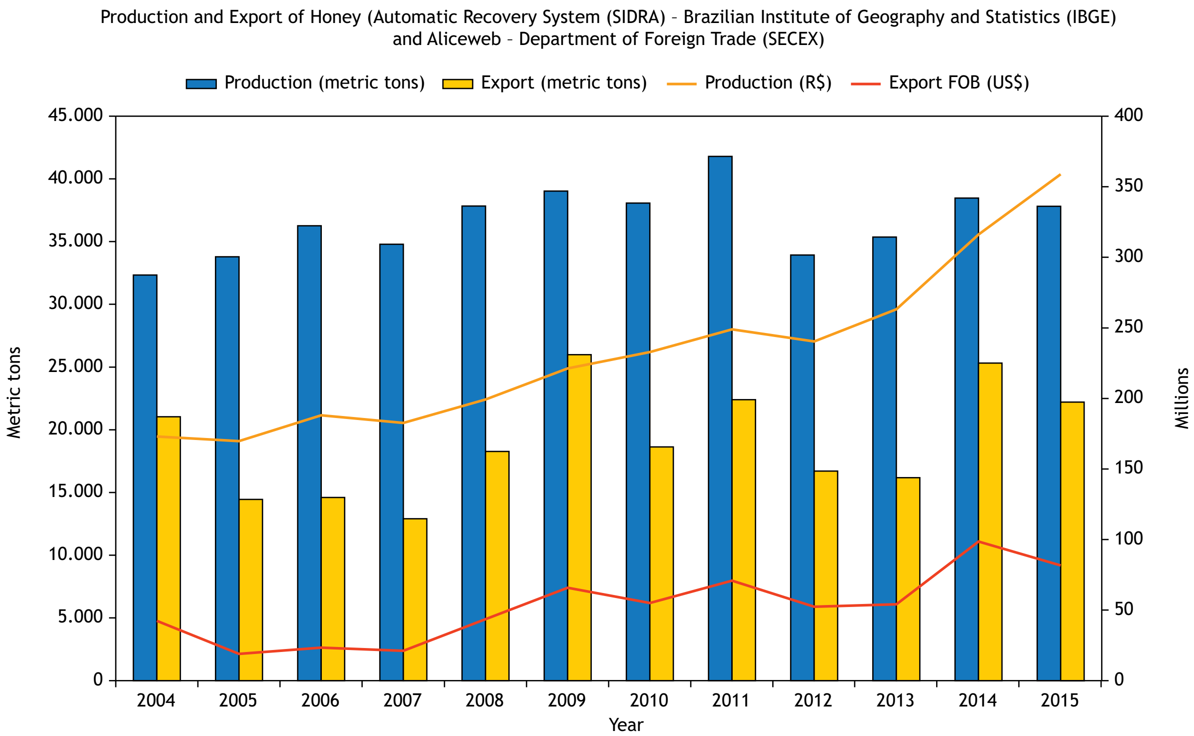
Chemical hazards present in honey, introduced by man during the management of bees, of which the following can be emphasized:

- Acaricides used for the control of mites such as *Varroa destructor*, which may be persistent synthetic agents such as cymiazole, fluvalinate, amitraz, flumethrin, and coumaphos; or natural nontoxic substances such as thymol, aqueous solution of lactic acid, aqueous solution of oxalic acid, and aqueous solution of formic acid;
- Antimicrobials used for the prevention of American foulbrood and European foulbrood, such as sulfonamides, aminoglycosides, tetracyclines, amphiphiles, macrolides, beta-lactams, and nitrofuran metabolites;
- Insecticides, such as paradichlorobenzene and naphthalene, for the control of wax moths;
- Repellents, such as phenol; however, caution should be exercised when assessing phenol, as it is a natural constituent of honey.

Despite several agents that have already been mentioned for use in beekeeping, the Brazilian Agricultural Research Corporation[3] discourages the use of chemical agents, either to avoid microbial resistance or to avoid the occurrence of residues in the hive. At the global level, however, the detection of residues of various agents not authorized for this species is common, such as those carried out in the European Union[25].

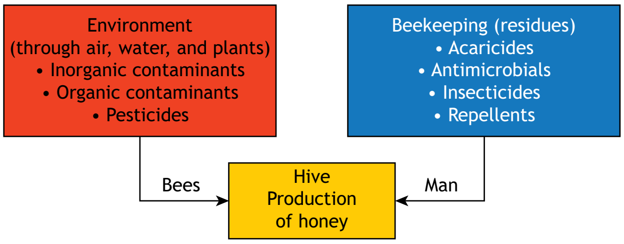
In the category of emerging residues, among veterinary drugs not authorized for use in hives, we highlight the class of quinolones, which are antimicrobials associated with hypersensitivity to[26,27,] and the development of, bacterial resistance[28,29]. Such residues have been found mainly in honey of Chinese origin, as seen in the *Rapid Alert System for Food and Feed* of the European Community[25].

Fluoroquinolones, also known as second-generation quinolones, have been classified by the World Health Organization as one of the four classes of antimicrobials critical for human health because of the risk of bacterial resistance, especially *Salmonella spp.* and *Escherichia coli* in animals. At the same time, fluoroquinolones are one of the few therapies for serious *Salmonella spp.* and *E.*



Source: Own elaboration.

Figure 1. Honey: Production (Brazilian Institute of Geography and Statistics) and Export (Department of Foreign Trade – SECEX) between 2004 and 2015.



Source: Adapted from Bogdanov[24].

Figure 2. Sources of chemical hazards for a bee colony.

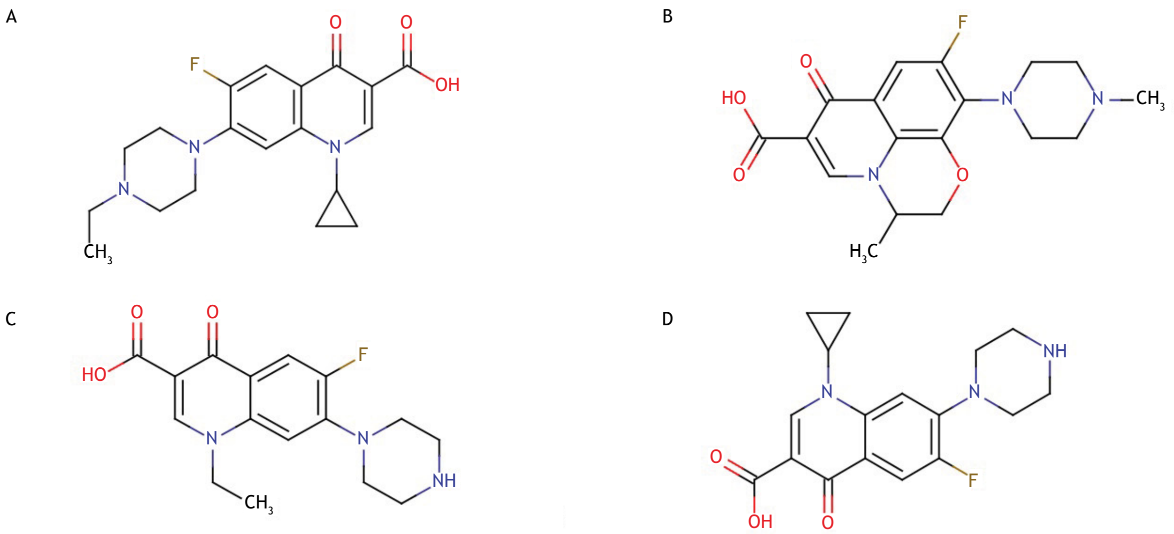
coli infections, the incidence of which, in humans, is high[30]. The *World Organization for Animal Health – Office International des Epizooties* – has also considered this class as critical because it has a wide range of therapeutic applications and it is critically important in the treatment of septicemia and enteric and respiratory diseases[31]. Some antimicrobials that represent this class are enrofloxacin, ofloxacin, norfloxacin, and ciprofloxacin (Figure 3).

In relation to contaminants, toxic natural substances may also occur, as they are secondary metabolites of plants used by bees in honey production. One of the major groups of substances in this situation, which may be considered as an emerging contaminant, is the group of pyrrolizidine alkaloids[33-35]. Pyrrolizidine alkaloids and their N-oxides are produced by more than 6,000 plant species, including representatives of the families Boraginaceae, Asteraceae, Fabaceae, Apocynaceae, and Orchidaceae, and more than 660 pyrrolizidine alkaloids have been isolated. Because of their toxicity to predators, such as insects and animals, these substances are also known as “natural pesticides”[36]. Prakash and Pereira[37] indicated this group of alkaloids as the leading group among plant toxins associated with adverse effects in humans and animals. In their work, they discuss toxicity in animals – carcinogenicity and pulmonary toxicity – and in humans – hepatotoxicity, teratogenicity, and carcinogenicity - because these substances, or their N-oxide derivatives, appear to react readily with nucleophilic cellular constituents, such as DNA. The *International Agency for Research on Cancer* of the *World Health Organization* have already evaluated several pyrrolizidine alkaloids and have classified three of them – lasiocarpine, monocrotaline, and rideline – as possibly carcinogenic to humans (group 2B)[38-40]. The pyrrolizidine nuclei, generally necine or otonecine, and other examples of pyrrolizidine alkaloids can be seen in Figure 4.

Some Brazilian authors have reported on the toxicity of pyrrolizidine alkaloids, especially in animals[41,42], but only one very recent article was found on the presence of this class of substances in honey in the country[43]. The authors of this paper developed and validated an analytical methodology that was applied to 92 honey samples. Ninety-nine percent of the samples showed the presence of at least three of the eight alkaloids researched. No articles have been found that describe the identification of quinolones in national honey by Brazilian researchers. However, there are several papers addressing the microbial resistance of this class of substances[44- 47].

When an international search is carried out, a different scenario is seen. In addition to the aforementioned articles addressing health risks related to pyrrolizidine alkaloids and quinolones, we also found several articles addressing strategies for detecting and analyzing both pyrrolizidine alkaloids[48-50] and quinolones[51-53 in honey]. This fact, in itself, shows the need to develop further scientific knowledge about these contaminants in Brazil.

When it comes to natural substances toxic to honey, the class of pyrrolizidine alkaloids may be the most-reported toxic class, but it is not the only one. Among the several other classes of phytotoxins that may be present in honey and lead to toxic effects[54] are the class of grayanotoxins, which are diterpenes with a tetracyclic A-nor-B-homo-ent-kaurane skeleton (Figure 5), produced



Source: Adapted from the Royal Society of Chemistry[32].

Figure 3. Enrofloxacin (a), Ofloxacin (b), Norfloxacin (c), and Ciprofloxacin (d).

as secondary metabolites by the genus *Rhododendron, Pieris (Andromeda), Leucothoe, Craibiodendron, Lyonia,* or *Kalmia*[55].

Among the toxic effects of grayanotoxins in humans are nausea, hypotension, bradycardia, and altered mental status[56-58]. Grayanotoxins may be present in honey produced in areas where the abovementioned genera are present and bloom, and their ingestion may lead to the toxic effects described[55].

More recently, a category of contaminants, usually found in other types of food, has also been found in honey: the organic migrants from packaging. Lo Turco and colleagues investigated the presence of 26 substances used in the production of plastic polymers, in addition to bisphenol A, in samples of honey from various flowering plants from Sicily and Calabria, in Italy, and although they did not find the presence of bisphenol A, they did find residues of various phthalates[59].

HEALTH SURVEILLANCE OF ANIMAL PRODUCTS: THE SITUATION OF HONEY

Public policies related to food safety issues are under the control of different agents involved in regulatory systems, and the VISA has its role defined by Law No. 9,782/99. In addition to the control of food, the control of drugs and cosmetics is the responsibility of the VISA, whose role is designed to control the risk of damage to the health of the population by protecting, preventing, and controlling diseases, and promoting health[60].

Although honey is used as food, as an ingredient in food, and in pharmaceutical and cosmetic formulations, health legislation, or even broader legislation, is negligible in the country. Brazilian legislation[2-4] only addresses definitions, labeling parameters, and physicochemical specifications, and the classification adopted by the National Health Surveillance Agency (ANVISA) is restricted to table honey, which meets all the specifications defined for this class, and industrial honey, but fails to meet at least one specification of table honey, while still meeting the specifications for industrial honey. The Brazilian pharmacopoeia[61] does not include a monograph on honey and the Brazilian homeopathic pharmacopoeia[62] does not even mention honey. The latter is restricted to the use of bees only (use of the intact insect) in formulations, this being one of the cases in which the animal species, and not plants, is used as raw material for the production of homeopathic medicines.

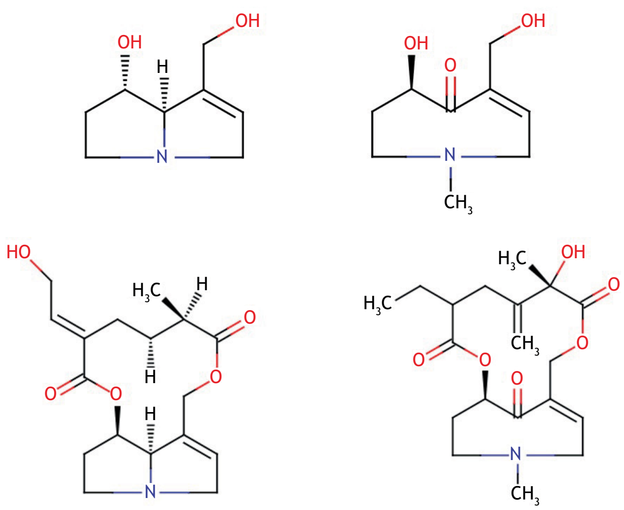
The European pharmacopoeia[63] and the Japanese pharmacopoeia[64] include monographs for honey, with physicochemical specifications similar to those found in national and international legislation. The United States pharmacopoeia[15] includes a monograph for purified honey in which, in addition to physicochemical specifications, there are microbiological parameters for total counts (1,000 CFU for bacteria and 100 CFU for molds and yeasts) and absence of pathogenic microorganisms, highlighting the absence of the *Clostridium* species.

The *Codex Alimentarius*, despite having a defined standard for the quality for honey[65], makes general considerations regarding residues and contaminants in this matrix, however, further research showed that maximum limits or tolerances on acceptable levels have not yet been established[66,67].

The *Joint Expert Committee on Food Additives* has not yet defined maximum residue limits or acceptable daily intake for honey[68]. The European community has also not established maximum residue limits for substances in honey[69], but it has established recommended concentration values for the development of analytical methods for substances that do not yet have maximum residue limits[70]; however, given the small number of substances, the scope is still less comprehensive than desirable.

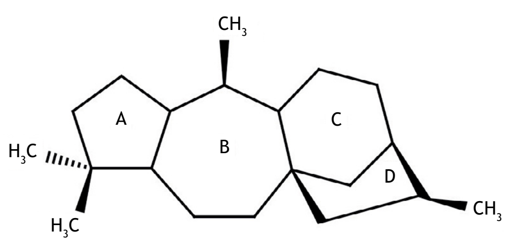
It is important to note that the specific legislation on pyrrolizidine alkaloids, specifically, is still emerging worldwide. Michel and Raezke[36] comment on the current situation in several countries:

- Germany: restriction of oral exposure to pyrrolizidine alkaloids and their N-oxides in pharmaceutical products derived from herbs at 1 µg/day for a maximum of six weeks annually;
- Australia and New Zealand: provisional daily intake limit of 1 µg/kg body weight daily;



Source: Adapted from the Royal Society of Chemistry[32].

Figure 4. Necine (above and left), Otonecine (above and right), Eruciflorine (below and left), and Emiline (below and right).



Source: Adapted from These and Bodi[55].

Figure 5. Basic chemical structure of various grayanotoxins.

- European Union: maximum exposure level of 4 µg/kg for echium oil;
- Netherlands: limit recommendation of 0.1 µg/100 g of food.

The same authors recommend the collection of more data on the presence of pyrrolizidine alkaloids, both by the industry and by analytical laboratories.

The same situation of incipient or non-existent legislation is observed in relation to the presence of other phytotoxins, such as grayanotoxins, in honey[54].

In Brazil, there are at least two major programs for the monitoring of contaminants and residues that have honey in their scope, among other types of food: the National Program for the Control of Residues of Veterinary Drugs in Food Exposed to Consumption (PAMVet) and the National Plan for the Control of Residues and Contaminants (PNCRC).

The PAMVet is conducted by ANVISA and it aims to assess the potential exposure of consumers to veterinary drug residues by ingesting commercially available animal food[71]. Although honey is in the scope, its monitoring has not been implemented so far, according to the schedule of the program.

The PNCRC is conducted by the Ministry of Agriculture, Livestock, and Food Supply and it aims to validate and evaluate good practices throughout the production chain, to verify the quality and the hygienic and sanitary safety factors of plant and animal products, their by-products, and derivatives of economic value, and to ensure a safe and innocuous system for consumers that meet international health requirements[72]. The PNCRC is subdivided into the PNCRC/Plant and the PNCRC/Animal, and the Honey Residue Control Program is included in the latter. Its guidelines and protocols are contained in the legislation of the PNCRC[73], and this program has initially monitored the antimicrobials tetracycline, oxytetracycline, chlortetracycline, sulfathiazole, sulfametazine, sulfadimethoxine, and the inorganic contaminants cadmium, lead, and arsenic. However, the monitoring scope has increased every year and, in 2014, it monitored 15 antimicrobials (including the classes of tetracyclines, sulfonamides, macrolides, nitrofurans, and chloramphenicol), 13 halogenated and organochlorine compounds, three carbamates, five pyrethroids, eight organophosphates, and three inorganic contaminants[74].

Despite the Brazilian effort regarding the monitoring of residues and contaminants, it should be noted that some classes of compounds, such as quinolones, are not yet addressed in the programs. Such antimicrobials should be prioritized because, in addition to being relatively toxic, they are directly related to the ability to induce bacterial resistance[75]. Neither pyrrolizidine alkaloids nor grayanotoxins are addressed in the Brazilian programs, and their relevance is related to their toxicities, as discussed. As it is the responsibility of ANVISA to establish residue and contaminant limits for animal food, it is essential to understand the risk of exposure of the consumer to the substances mentioned in this article so that decisions can be supported, in order to manage, minimize or eliminate this risk.

The presence of residues of substances used in the production of plastic polymers is addressed by ANVISA and has a history of revision and updating of the legislation, with Resolution RDC # 56, November 16, 2012 being in force[76]. This resolution provides a positive list of monomers, other initiating substances, and polymers authorized for the manufacture of packaging and plastic equipment in contact with food, and it also gives the specific migration limits for the various substances listed. However, the evaluation of specific migration limits of plasticizers is not covered by the monitoring programs that include honey.

CONCLUSION

The research and monitoring of residues and contaminants in honey are extremely important as they address both the issues of food safety and therapeutic safety of a medicinal, pharmaceutical, and cosmetic animal product, which is a large part of the role of VISA.

This monitoring, currently carried out by the PNCRC and also proposed by PAMVet, needs constant updating of its scope to meet current demands and the demands related to emerging contaminants.

Currently, none of these programs provides for the monitoring of quinolones or phytotoxins, such as pyrrolizidine alkaloids and grayanotoxins.

Quinolones are a class of antimicrobials that, in addition to being associated with hypersensitivity reactions, are linked to the issue of bacterial resistance, one of the world's biggest public health problems.

Pyrrolizidine alkaloids, grayanotoxins, and other phytotoxins are secondary plant metabolites used by bees to produce honey, thus being an integral part of the "raw material" used. These substances have already had their toxicity extensively discussed in the literature and they may represent a health risk, as we know that they occur in honey, in addition to the plants that produce them.

For the emerging contaminants covered here, scientific publications with national data are scarce or non-existent in relation to honey, indicating that the development of new scientific knowledge is needed in this area.

Further study is recommended on the occurrence of quinolones, pyrrolizidine alkaloids, grayanotoxins, and substances used in the production of plastic polymers in honey in Brazil, so that potential health risks from the consumption of honey containing these substances are known and minimized or eliminated, and human health can thus be protected.

REFERENCES

1. Rother ET. Revisão sistemática X revisão narrativa. Acta Paul Enferm. 2007;20(2):v-vi. https://doi.org/10.1590/S0103-21002007000200001
2. Ministério da Agricultura e Abastecimento (BR). Instrução Normativa N°11, de 20 de outubro de 2000. [Regulamento Técnico de Identidade e Qualidade do Mel]. Diário Oficial União. 23 out 2000.
3. Embrapa. Sistemas de produção. Produção de mel 2003. Brasília, DF: Embrapa; 2003[acesso 19 abr 2014]. Disponível em: http://sistemasdeproducao.cnptia.embrapa.br/FontesHTML/Mel/SPMel/index.htm
4. Ministério da Saúde (BR). Resolução Nº 12, de 24 de julho de 1978. Normas Técnicas Especiais – Mel. Diário Oficial União. 24 jul 1978.
5. Sociedade Brasileira de Farmacognosia. Análise do mel. Curitiba: Sociedade Brasileira de Farmacognosia; 2014[acesso 19 abr 2014]. Disponível em: http://www.sbfgnosia.org.br/Ensino/analise_mel.html
6. Krell R. Value-added Products from beekeeping. Rome: Food and Agriculture Organization of the United Nations; 1996. (FAO Agricultural services bulletin, vol 124).
7. Al-Waili NS, Salom K, Butler G, Al Ghamdi AA. Honey and microbial infections: a review supporting the use of honey for microbial control. J Med Food. 2011;14(10):1079-96. https://doi.org/10.1089/jmf.2010.0161
8. Burlando B, Cornara L. Honey in dermatology and skin care: a review. J Cosmet Dermatol. 2013;12(4):306-13. https://doi.org/10.1111/jocd.12058
9. Erejuwa OO, Sulaiman SA, Wahab MS. Oligosaccharides might contribute to the antidiabetic effect of honey: a review of the literature. Molecules. 2012;17(1):248-66. https://doi.org/10.3390/molecules17010248
10. Molan PC. Why honey is effective as a medicine. 1. Its use in modern medicine. Bee World. 1999;80(2):80-92. https://doi.org/10.1080/0005772X.1999.11099430
11. Molan PC. Why honey is effective as a medicine. 2. The scientific explanation of its effects. Bee World. 2001;82(1):22-40. https://doi.org/10.1080/0005772X.2001.11099498
12. Bang LM, Buntting C, Molan P. The effect of dilution on the rate of hydrogen peroxide production in honey and its implications for wound healing. J Altern Complement Med. 2003;9(2):267-73. https://doi.org/10.1089/10755530360623383
13. Apitherapy News. FDA approves honey wound care products. 15 jul 2012[acesso 17 maio 2014]. Disponível em: http://apitherapy.blogspot.com.br/2012/07/fda-approves-honey-wound-care-products.html
14. Walker L. FDA quietly acknowledges medical benefits of honey. 2008 Mar 21[acesso 17 maio 2014]. Disponível em: http://www.naturalnews.com/022872_honey_FDA_benefits.html
15. U.S. Pharmacopeial Convention. USP 39 NF 34: United States pharmacopeia and national formulary: Supplement 1. Rockville: U.S. Pharmacopeial Convention; 2016.
16. Destruti ABCB. Noções básicas de farmacotécnica. São Paulo: Editora SENAC; 1999.
17. Buainain AM, Batalha MO, coordenadores. Cadeias produtivas de flores e mel. Ministério da Agricultura, Pecuária e Abastecimento/Instituto Interamericano de Cooperação para a Agricultura; 2007. (Série Agronegócios, vol 9).
18. Gebrim S. Produção de mel cresce 30% no último ano. Notícias. 2011[acesso 18 maio 2014]. Disponível em: http://www.agricultura.gov.br/animal/noticias/2011/03/producao-de-mel-cresce-30porcento-no-ultimo-ano
19. Cuba G. Dados de exportações de mel. Inteligência Comercial. 2014[acesso 18 maio 2014. Disponível em: http://www.beebrazil.com/inteligencia_comercial_abemel_abril.pdf
20. Cuba G. Setor apícola brasileiro em números. Inteligência Comercial. 16 jul 2015[acesso 25 out 2015]. Disponível em: http://brazilletsbee.com.br/inteligencia_comercial_abemel_junho_2015.pdf
21. Instituto Brasileiro de Geografia e Estatística – IBGE. Sistema IBGE de Recuperação Automática – SIDRA. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística; 2016[acesso 2 out 2016]. Disponível em: http://www.sidra.ibge.gov.br/
22. Ministério do Desenvolvimento, Indústria e Comércio Exterior (BR). AliceWeb. Brasília, DF: Ministério do Desenvolvimento, Indústria e Comércio Exterior; 2016[acesso 2 out 2016]. Disponível em: http://aliceweb.mdic.gov.br/
23. O salto do mel. SEBRAE Agronegócios. 2006(3):10-11.
24. Bogdanov S. Contaminants of bee products. Apidologie. 2006;37(1):1-18. https://doi.org/10.1051/apido:2005043
25. European Commission. RASFF Portal. 2015[acesso 25 out 2015]. Disponível em: https://webgate.ec.europa.eu/rasff-window/portal/
26. Hadimeri H, Almroth G, Cederbrant K, Eneström S, Hultman P, Lindell A. Allergic nephropathy associated with norfloxacin and ciprofloxacin therapy. Report of two cases and review of the literature. Scand J Urol Nephrol. 1997;31(5):481-5. https://doi.org/10.3109/00365599709030647
27. Lobera T, Audícana MT, Alarcón E, Longo N, Navarro B, Muñoz D. Allergy to quinolones: low cross-reactivity to levofloxacin. J Investig Allergol Clin Immunol. 2010;20(7):607-11.
28. Jacoby GA. Mechanisms of resistance to quinolones. Clin Infect Dis. 2005;41(Suppl 2):S120-6. https://doi.org/10.1086/428052
29. Strahilevitz J, Jacoby GA, Hooper DC, Robicsek A. Plasmid-mediated quinolone resistance: a multifaceted threat. Clin Microbiol Rev. 2009;22(4):664-89. https://doi.org/10.1128/CMR.00016-09

30. World Health Organization – WHO. Critically important antimicrobials for human medicine. 3rd rev. Geneva: World Health Organization; 2012.

31. World Organization for Animal Health. OIE list of antimicrobial agents of veterinary importance. Paris: World Organization for Animal Health; 2015.

32. Royal Society of Chemistry. ChemSpider: search and share chemistry. 2015[acesso 11 set 2015]. Disponível em: http://www.chemspider.com/

33. Boppré M. The ecological context of pyrrolizidine alkaloids in food, feed and forage: an overview. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2011;28(3):260-81. https://doi.org/10.1080/19440049.2011.555085

34. Edgar JA, Colegate SM, Boppré M, Molyneux RJ. Pyrrolizidine alkaloids in food: a spectrum of potential health consequences. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2011;28(3):308-24. https://doi.org/10.1080/19440049.2010.547520

35. Kempf M, Wittig M, Schönfeld K, Cramer L, Schreier P, Beuerle T. Pyrrolizidine alkaloids in food: downstream contamination in the food chain caused by honey and pollen. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2011;28(3):325-31. https://doi.org/10.1080/19440049.2010.521771

36. Michel R, Raezke KP. Pyrrolizidine alkaloids in honey: brief overview regarding de occurrence, toxicological effects and risk assessment. Bremen: Intertek Food Services; 2009.

37. Prakash AS, Pereira TN, Reilly PEB, Seawright AA. Pyrrolizidine alkaloids in human diet. Mutat Res. 1999;443(1-2):53-67. https://doi.org/10.1016/S1383-5742(99)00010-1

38. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monogr Eval Carcinog Risks Hum. 2002;82:1-556.

39. Beuerle T, Benford D, Brimer L, Cottrill B, Doerge D, Dusemund B et al. Scientific opinion on pyrrolizidine alkaloids in food and feed: EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA J. 2011;9(11):2449. https://doi.org/10.2903/j.efsa.2011.2406

40. World Health Organization, International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risk of chemicals to man. Lyon: International Agency for Research on Cancer, 1976[acesso 13 fev 2017]. Vol. 10: Some naturally occurring substances. 1976. Disponível em: http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono10.pdf

41. Lucena RB, Rissi DR, Maia LA, Flores MM, Dantas AFM, Nobre VMdT, et al. Intoxicação por alcaloides pirrolizidínicos em ruminantes e equinos no Brasil. Pesq Vet Bras. 2010;30(5):447-52. https://doi.org/10.1590/S0100-736X2010000500013

42. Sandini TM, Udo MSB, Spinosa HDS. *Senecio brasiliensis* e alcaloides pirrolizidínicos: toxicidade em animais e na saúde humana. Biotemas. 2013;26(2):83-92. http://dx.doi.org/10.5007/2175-7925.2013v26n2p83

43. Valese AC, Molognoni L, Ploêncio LAS, Lima FG, Gonzaga LV, Górniak SL et al. A fast and simple LC-ESI-MS/MS method for detecting pyrrolizidine alkaloids in honey with full validation and measurement uncertainty. Food Control. 2016;67:183-91. https://doi.org/10.1016/j.foodcont.2016.02.050

44. Barros RR, Kegele FCO, Paula GR, Brito MA, Duarte RS. Molecular characterization of the first fluoroquinolone resistant strains of *Streptococcus agalactiae* isolated in Brazil. Braz J Infect Dis. 2012;16(5):476-8. https://doi.org/10.1016/j.bjid.2012.05.003

45. Ferreira WA, Ferreira CM, Naveca FG, Almeida NC, Vasconcelos WS, Gomes JS et al. Genotyping of two *Neisseria gonorrhoeae* fluroquinolone-resistant strains in the Brazilian Amazon Region. Mem Inst Oswaldo Cruz. 2011;106(5):629-31. https://doi.org/10.1590/S0074-02762011000500018

46. Ito CAS, Gales AC, Tognim MCB, Munerato P, Dalla Costa LM. Quinolone-resistant *Escherichia coli*. Braz J Infect Dis. 2008;12(1):5-9. https://doi.org/10.1590/S1413-86702008000100003

47. Pereira AS, Andrade SS, Monteiro J, Sader HS, Pignatari ACC, Gales AC. Evaluation of the susceptibility profiles, genetic similarity and presence of qnr gene in *Escherichia coli* resistant to ciprofloxacin isolated in Brazilian hospitals. Braz J Infect Dis. 2007;11(1):40-3. https://doi.org/10.1590/S1413-86702007000100011

48. Betteridge K, Cao Y, Colegate SM. Improved method for extraction and LC-MS analysis of pyrrolizidine alkaloids and their N-oxides in honey: application to *Echium vulgare* honeys. J Agric Food Chem. 2005;53(6):1894-902.

49. Griffin CT, O'Mahony J, Danaher M, Furey A. Liquid chromatography tandem mass spectrometry detection of targeted pyrrolizidine alkaloids in honeys purchased within Ireland. Food Anal Methods. 2015;8(1):18-31. https://doi.org/10.1007/s12161-014-9855-1

50. Martinello M, Cristofoli C, Gallina A, Mutinelli F. Easy and rapid method for the quantitative determination of pyrrolizidine alkaloids in honey by ultra performance liquid chromatography-mass spectrometry: an evaluation in commercial honey. Food Control. 2014;37:146-52. https://doi.org/10.1016/j.foodcont.2013.09.037

51. Beretta G, Artali R, Caneva E, Orlandini S, Centini M, Facino RM. Quinoline alkaloids in honey: further analytical (HPLC-DAD-ESI-MS, multidimensional diffusion-ordered NMR spectroscopy), theoretical and chemometric studies. J Pharm Biomed Anal. 2009;50(3):432-9. https://doi.org/10.1016/j.jpba.2009.05.029

52. Durden DA, Fernandes G. Quantitation of fluoroquinolones in honey using tandem mass spectrometry (LC-MS/MS): nested validation with two mass spectrometers. J AOAC Int. 2010;93(5):1633-55.

53. Mottier P, Hammel YA, Gremaud E, Guy PA. Quantitative high-throughput analysis of 16 (Fluoro)quinolones in honey using automated extraction by turbulent flow chromatography coupled to liquid chromatography-tandem mass Spectrometry. J Agric Food Chem. 2008;56(1):35-43. https://doi.org/10.1021/jf072934d

54. Islam MN, Khalil MI, Islam MA, Gan SH. Toxic compounds in honey. J Appl Toxicol. 2014;34(7):733-42. https://doi.org/10.1002/jat.2952
55. These A, Bodi D, Uecker S, Reimers K, Ronczka S, Preiss-Weigert A, et al. A case of human poisoning by grayanotoxins following honey ingestion: elucidation of the toxin profile by mass spectrometry. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2015;32(10):1674-84. https://doi.org/10.1080/19440049.2015.1042410
56. Gunduz A, Turedi S, Russell RM, Ayaz FA. Clinical review of grayanotoxin/mad honey poisoning past and present. Clin Toxicol (Phila). 2008;46(5):437-42. https://doi.org/10.1080/15563650701666306
57. Jansen SA, Kleerekooper I, Hofman ZL, Kappen IF, Stary-Weinzinger A, Heyden MA. Grayanotoxin poisoning: 'mad honey disease' and beyond. Cardiovasc Toxicol. 2012;12(3):208-15. https://doi.org/10.1007/s12012-012-9162-2
58. Lampel KA, Al-Khaldi S, Cahill SM, editors. Bad bug book: handbook of foodborne pathogenic microorganisms and natural toxins. Silver Spring: U.S. Food and Drug Administration; 2012.
59. Lo Turco V, Di Bella G, Potortì AG, Tropea A, Casale EK, Fede MR et al. Determination of plasticisers and BPA in Sicilian and Calabrian nectar honeys by selected ion monitoring GC/MS. Food Addit Contam Part A Chem Anal Cotnrol Expo Risk Assess. 2016;33(11):1693-9. https://doi.org/10.1080/19440049.2016.1239030
60. Brasil. Lei Nº 9.782, de 26 de janeiro de 1999. Define o Sistema Nacional de Vigilância Sanitária, cria a Agência Nacional de Vigilância Sanitária e dá outras providências. Diário Oficial União. 27 jan 1999.
61. Agência Nacional de Vigilância Sanitária – Anvisa. Farmacopeia brasileira. 5a ed. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2010.
62. Agência Nacional de Vigilância Sanitária – Anvisa. Farmacopeia homepática brasileira. 3a ed. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2011.
63. Council of Europe. European Pharmacopoeia Commission. European pharmacopoeia. Strasbourg: Council Of Europe; 2014.
64. Pharmaceutical and Medical Device Regulatory Science Society of Japan. The Japanese pharmacopoeia: English version. Tokyo: Pharmaceutical and Medical Device Regulatory Science Society of Japan; 2012.
65. Codex Alimentarius Commission. Revised codex standard for honey: Codex Stan 12-1981, Rev 1 (1987), Rev. 2 (2001). Rome: FAO; 2001.
66. Codex Alimentarius Commission. Maximum residue limits for veterinary drugs in foods. Rome: FAO; 2012.
67. Codex Alimentarius Commission. CODEX Online Commodity Categories. Pesticide residues in food and feed. Rome: FAO; 2014.
68. Food and Agriculture Organization of the United Nations, World Health Orgtanization. Evaluation of certain veterinary drug residues in food: seventieth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization; 2009. (Technical report series, vol 954).
69. União Européia. UE 37/2010: Regulamento da Comissão relativo a substâncias farmacologicamente activas e respectiva classificação no que respeita aos limites máximos de resíduos nos alimentos de origem animal. Eur-Lex. 2010.
70. Community Reference Laboratories. CRLs view on state of the art analytical methdos for national residue control plans. Chicago: Community Reference Laboratories; 2007.
71. Agência Nacional de Vigilância Sanitária – Anvisa. Plano Nacional de Análise de resíduos de medicamentos veterinários em alimentos expostos ao consumo - PAMVet Brasília, DF: Agência Nacional de Vigilância Sanitária; 2003.
72. Ministério da Agricultura, Pecuária e Abastecimento (BR). Plano Nacional de Controle de Resíduos e Contaminantes. Brasília, DF; 2014[acesso 25 maio 2014]. Disponível em: http://www.agricultura.gov.br/portal/page/portal/Internet-MAPA/pagina-inicial/pncrc
73. Ministério da Agricultura e do Abastecimento (BR). Instrução Normativa nº 42, de 22 de dezembro de 1999. Alterar o Plano Nacional de Controle de Resíduos em Produtos de Origem Animal –PNCR e os Programas de Controle de Resíduos em Carne – PCRC, Mel – PCRM, Leite – PCRL e pescado – PCRP. Diário Oficial União. 22 dez 1999;Seção 1:213.
74. Ministério da Agricultura, Pecuária e Abastecimento (BR). Instrução Normativa Nº 13, de 15 de julho de 2015. Publica o Subprogramas de Monitoramento e Subprograma Expoloratório do Plano Nacional de Controle de Resíduos e Contaminantes. Diário Oficial União. 20 jul 2015;Seção 1:5-12.
75. Asselt ED, Spiegel M, Noordam MY, Pikkemaat MG, Fels-Klerx HJ. Risk ranking of chemical hazards in food: a case study on antibiotics in the Netherlands. Food Res Int. 2013;54(2):1636-42. https://doi.org/10.1016/j.foodres.2013.08.042
76. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC Nº 56, de 16 de novembro de 2012. Dispõe sobre a lista positiva de monômeros, outras substâncias iniciadoras e polímeros autorizados para a elaboração de embalagens e equipamentos plásticos em contato com alimentos. Diário Oficial União. 21 nov 2012.

Conflict of interest
The authors report that there is no potential conflict of interest with peers and institutions, political or financial, in this study.