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Review

Acrylamide: A review about its toxic effects in the light of Developmental Origin of Health and Disease (DOHaD) concept

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ABSTRACT

The endocrine system is highly sensitive to endocrine-disrupting chemicals (EDC) which interfere with metabolism, growth and reproduction throughout different periods of life, especially in the embryonic and pubertal stages, in which gene reprogramming may be associated with impaired development and control of tissues/organs even in adulthood. Acrylamide is considered a potential EDC and its main source comes from fried, baked and roasted foods that are widely consumed by children, teenagers and adults around the world. This review aimed to present some aspects regarding the acrylamide formation, its toxicokinetics, the occurrence of acrylamide in foods, the recent findings about its effects on different systems and the consequences for the human healthy. The challenges to characterize the molecular mechanisms triggered by acrylamide and to establish safe levels of consumption and/or exposure are also discussed in the present review.

1. Introduction

It is now known that various endocrine abnormalities may be related to the presence of the EDCs in the environment. EDCs are exogenous substances found in the air, water, food and other consumer products that may interfere with the endocrine system by impairing the production, release, metabolism, excretion or still mimicking the endogenous hormonal activity. In this manner, EDCs may cause dysfunctions during the developmental phase, modify the behavior and disturb the reproduction, compromising several aspects of human health (WHO/UNEP, 2013). Therefore, changes caused by these substances constitute a major public health problem, since exposure to different chemical compounds has become more frequent (Casals-Casas & Desvergne, 2011; Diamanti-Kandarakis et al., 2009; Foulds, Trevino, York, & Walker, 2017; Nadal, Quesada, Tuduri, Nogueiras, & Alonso-Magdalena, 2017).

In a very similar way to the endogenous hormones, EDCs triggered some actions in low doses, however, they do not show a classic toxicology standard and sometimes its effects can be observed as U-dose-response (maximum responses at low and high doses) or inverted U (maximum effects observed at intermediate doses) that are not observed with another drugs due to the dynamics features of receptor occupancy and saturation (Vandenberg et al., 2012). In this sense, lower doses could induce stronger toxic effects than higher doses, hindering the determination of certain parameters such as LOAEL (Lowest Observed Adverse Effect Level) and NOAEL (No Observed Adverse Effect Level – a higher dose that does not result in a toxic effect) for the endocrine disruption effects (Diamanti-Kandarakis et al., 2009; Schug, Janesick, Blumberg, & Heindel, 2011; Vandenberg, 2014; Weiss, 2011; Welshons et al., 2003). Another factor that may be considered is the age or the period of life in which individuals are exposed to endocrine deregulators. The developmental embryonic period and the pre-puberty are the most susceptible to disruptions. In these both periods, the hormones are directly involved in the control and development of tissues and organs, including the reproductive, immune and nervous systems (de Cock, de Boer, Lamoree, Legler, & van de Bor, 2014; Stoker, Parks, Gray, & Cooper, 2000). Thus, the fetus, children and teenagers are more susceptible to greater risks when exposed to these substances and hormonal imbalances in these periods could lead to hormonal disorders in adults (Solomon & Schettler, 2000), supporting the Developmental Origin of Health and Disease (DOHaD) concept (Barouki et al., 2018).

In this context, acrylamide presents an endocrine-disrupting potential. The main acrylamide exposure source are some foods after heating processes, being widely found in bakery products as breads, biscuits, toast, coffee, french fries or potato chips (Arisseto & Toledo,

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2008; Friedman, 2003). It is worth mentioning that french fries, cookies and morning cereals are products usually consumed by children and adolescents, representing a population that is frequently exposed to the substance (Hilbig, Freidank, Kersting, Wilhelm, & Wittsiepe, 2004; Lambert et al., 2018; Mojska, Gielecinska, & Stos, 2012). In addition, children generally ingest 2–3-fold times food consumption, measured by food mass/body weight, compared to adults (FAO/WHO, 2002). Recent reports have shown that individuals between 12 and 21 years old are 2–3 times more sensitive to EDCs (McMullen, Ghassabian, Kohn, & Trasande, 2017). Supporting the hypothesis of acrylamide acting as an endocrine-disrupting chemical, Lai et al. (2017) recently demonstrated that the acrylamide administration during the pregnancy triggers toxic dose-dependent effects on growth and development of hippocampal neurons of recently weaned rats.

Considering the paramount role of thyroid hormones in the human growth and development during childhood and adolescence, an special attention needs to be highlighted regarding the acrylamide exposure effects at these stages of life and the consequences on neuroendocrine system (Boas, Feldt-Rasmussen, & Main, 2012; de Cock et al., 2014; Duke, Ruestow, & Marsh, 2018; FAO/WHO, 2005; Lambert et al., 2018).

2. Acrylamide

Acrylamide is a solid monomer, which shows a white coloration with features crystalline and odorless. Its chemical structure presents a polar amide group and a vinyl function, which allows the acrylamide polymerization. The acrylamide is a reactive α,β-carbonyl unsaturated molecule, usually obtained from the hydration of acrylonitrile by sulfuric acid monohydrate at 90 or 100 °C and has been commercially produced by industry since 1950. Acrylamide, also known as 2-propenamide (CAS No. 79-06-1), presents 71.08 Molecular Weight (MW) and its molecular formula is C3H5ON which molecular structure is shown in Fig. 1 (Arisseto & Toledo, 2008; EPA Environmental Protection Agency, 1994; Weiss, 2002).

The scientific community interest regarding acrylamide occurred after the environmental tragedy during the tunnels construction for the high-speed railways in Sweden (1997), in which workers were exposed to acrylamide-containing sealants during the accident (Hagmar et al., 2001). Afterwards, the presence of Acrylamide-Hemoglobin (Hb) adducts, considered as an acrylamide bioindicator, was evaluated in their blood samples and compared to control groups. A clear dose-response was found between the Hb-adduct levels and deteriorated symptoms of the peripheral nervous system (PNS) that were reversed 18 months after the cessation of exposure (Hagmar et al., 2001).

In addition, previous studies performed in blood samples of laboratory workers, smokers and nonsmokers that were using polyacrylamide gels in their researchers have shown that the acrylamide adducts were detected in all persons (Bergmark, 1997). A significantly increased in the Hb-adduct was observed in smokers and it was correlated to the number of cigarettes smoked per day. Surprisingly, a high background of acrylamide adducts was detected in nonsmoking control group, suggesting that other possible sources of acrylamide should be investigated as food, beverages or endogenous metabolites (Bergmark, 1997).

Acrylamide is widely used in the synthesis of polyacrylamides related to several applications, as polyacrylamide gel for electrophoresis in research laboratories, flocculating agent to clarify and purify drinking water, in the sewage treatment, in the soil conditioning for the dams production and as a sealing agent in civil buildings. Moreover, acrylamide has been used in the paper, wood and textile industries and its residues are also found in cosmetics, toiletries and cigarettes. Indeed, the cigarette smoke presents about 1.1–2.34 μg of acrylamide per cigarette, being acrylamide a component of tobacco (Ma et al., 2009; Paulsson, Granath, Grawé, Ehrenberg, & Törnqvist, 2001; Shen et al., 2012; Weiss, 2002), however, the main source of human acrylamide contamination is found in some heated foods (Hileman, 2002; Tareke, Rydberg, Karlsson, Eriksson, & Törnqvist, 2000).

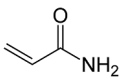

Fig. 1. Acrylamide molecular structure (NCBI, 2018).

The acrylamide formation by heating was confirmed through the identification of hemoglobin adducts of acrylamide in blood samples of rats fed with fried chow at 200 °C (Tareke et al., 2000) or with processed foods at high temperatures (Tareke, Rydberg, Karlsson, Eriksson, & Törnqvist, 2002). Thus, fried, baked and roasted foods favor the formation of acrylamide that occurs due to chemical reactions between nutrients (FDA, 2004). In Sweden, the National Food Agency conducted the first determination of acrylamide on commercial food products, followed by other in European countries and USA that confirmed the presence of this contaminant in several food products. Potato chips, french fries, toasts, cookies, breakfast cereals and coffee presented the highest levels of acrylamide (FDA, 2004).

In view of this, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) reported the occurrence of acrylamide in food supplies and highlighted its harmful effects on human health and the urgent need to reduce the acrylamide levels in food. In addition, it was shown that acrylamide levels ranged from 30 to 3500 μg/kg of body weight (BW), even between the same type of food (FAO/WHO, 2002).

In Brazil, around 2004 and 2006, the acrylamide levels were evaluated in 111 samples of 19 different types of foods. The levels ranged from lower than 20 μg/kg up to 2528 μg/kg, depending on the type of product. The highest levels were found in french fries, potato chips and potato sticks (144–2528 μg/BW kg). Coffee, toasts, water salt and cream cracker wafers also showed high acrylamide levels (Arisseto & Toledo, 2008).

Considering the dietary habits data obtained from 17 countries, with the exception of Latin America and Africa, the JECFA estimated 0.3–2.0 μg acrylamide intake/BW kg/day for average consumers and up to 5.1 μg acrylamide intake/BW kg/day for large consumers, and being the acrylamide intake by children was 2–3 fold greater than adults values. About 1 μg acrylamide intake/BW kg/day was established for average consumers and 4 μg/BW kg/day for large consumers. JECFA also reported that the relative contribution *per* food to the total ingestion values are 6–30% for french fries, 6–46% for potatoes chips, 13–39% for coffee and 10–30% for baked goods (FAO/WHO, 2005).

3. Formation of acrylamide in foods

Acrylamide is formed in the Maillard reaction, a non-enzymatic darkening or non-enzymatic glycation of proteins reaction, it occurs between the amino residue (−NH2) of aminoacids (proteins) and the carbonyl (C═O) from a reducing sugar (carbohydrates) when heat above 120 °C (Stadler et al., 2002). The asparagine is the main amino acid involved in the acrylamide formation while glucose, fructose, maltose and lactose are the principal sugars (Robert et al., 2004; Yaylayan & Stadler, 2005). The molecules rearrangements (called Amadori rearrangement) during the reaction steps consist of glycosylamine isomerizations, there is also the formation of the Schiff base (initial product of glucose and asparagine reaction), the degradation of Strecker and several intermediate reactions of which the hydroxymethyl furfural, that, in turn, originates the melanoidin (brown pigment) after polymerization and is responsible for the characteristic aspect/color of french fries and roasted foods (Robert et al., 2004; Vinci, Mestdagh, & De Meulenaer, 2012; Yaylayan & Stadler, 2005).

However, the full information regarding the relative importance of three possible routes to formation of acrylamide is still unknown. It is well documented that in a glucose/asparagine system, the glucos-1-yl-asparagine undergoes decarboxylation prior to its rearrangement into

Amadori product, to generate N-(D-glucos-1-yl)-3′-aminopropionamide; this intermediate in turn can undergo Amadori rearrangement to produce N-(1-deoxy-D-fructos-1-yl)-3′-aminopropionamide. Both aminopropionamide intermediates are capable of generating acrylamide directly or through formation of free 3-aminopropionamide (Perez Locas & Yaylayan, 2008). In addition, several factors affect the formation of acrylamide, such as temperature, warm-up time, humidity, amino acids concentration (asparagine) and the presence of reducing sugars in foods (Vinci et al., 2012).

4. Acrylamide toxicokinetics

Although the data regarding the acrylamide toxicokinetics in humans are scarce, it is known that its absorption occurs through dermal, respiratory and digestive systems. After oral absorption, the acrylamide is widely distributed for different tissues (Calleman, 1996) and in rats the highest percentages of this compound were found in muscle (48%), skin (15%), blood (12%) and liver (7%), while less than 1% was located in brain and spinal cord (Miller, Carter, & Sipes, 1982). The acrylamide is able to cross the placental barrier in humans and its presence in breast milk have also been detected (Sörgel et al., 2002).

Acrylamide is metabolized by the action of the cytochrome CYP2E1 enzyme, which gives rise to a highly reactive epoxide, the glycidamide (Kadry, Friedman, & Abdel-Rahman, 1999). Alternatively, acrylamide can be conjugated to glutathione, by glutathione-S-transferase enzyme, and the metabolite is excreted as mercapturic acid via the urinary route, as found in the urine of exposed workers (Fennell & Friedman, 2005). Small amounts can also be detected in feces and in exhaled air (Fennell & Friedman, 2005). In rodents, the bioavailability ranges from 23 to 48% when treated with 0.1 mg acrylamide/BW kg (administered in the diet for 30 min) and the removal occurs about 2 h later (Kadry et al., 1999; Miller et al., 1982). In humans the half-life is about 4 to 6 h (Calleman, 1996).

Glycidamide reacts with DNA molecules forming purine base adducts. Both glycidamide and acrylamide covalently binds to the valine terminal hemoglobin and form adducts that have been used as bioindicators or exposure markers (FAO/WHO, 2005; Hagmar et al., 2001). Acrylamide induces acute toxic effects when the oral doses are greater than 100 mg/kg of BW, and lethal doses are usually higher than 150 mg/kg of BW (FAO/WHO, 2005).

5. Effects on reproduction

Studies conducted in females fed for 6 weeks with acrylamide in the diet showed reduction of ovarian weight and oocyte development compared to control animals. The acrylamide-treated females presented increased reactive oxygen species (ROS), early apoptosis and reduced DNA and histone methylation levels resulting in reduced oocyte quality and fertility (Duan et al., 2015). In addition, acrylamide-treated oocytes showed impaired meiotic division characterized by reduction in the meiotic spindle mass and increases on chromosome rupture (Aras, Cakar, Ozkavukcu, Can, & Cinar, 2017). The involvement of oxidative stress on acrylamide toxicity was also described in Leydig and Sertoli cells which presented a decrease in the cell viability and increase in ROS and apoptosis, which was evidenced by the increase in the expression of apoptotic genes, as caspase3, *Bcl-2*, *Bax*, and *p53* (Yilmaz, Yildizbayrak, Aydin, & Erkan, 2017). Leydig cells cultured in media containing glycidamide showed a decrease in progesterone synthesis due to apoptosis induced by ROS (Li et al., 2017).

Prenatal exposure to acrylamide in porcine model reduced the number of ovarian follicles inducing follicular atresia by oocyte apoptosis (Hułas-Stasiak, Dobrowolski, Tomaszewska, & Kostro, 2013). A similar finding was observed in female mice, in which the acrylamide effects were correlated to dose-dependent increases in nitric oxide synthase (NOS) signaling (Wei, Li, Li, Zhang, & Shi, 2014). Male rats treated with acrylamide at the doses of 0.5 and 10 mg/kg/day for 8 weeks presented growth delay, reduced sperm reserves in the epididymis and histopathological lesions in the testes, suggesting partial depletion of germ cells (Wang et al., 2010). The administration of acrylamide (1 μg/ml) for six months to male rodents, a dose equivalent to 10.5 μg acrylamide/kg BW/day for humans, led to DNA damage in sperm, without affecting overall fertility. Male offspring also presented significantly increase on DNA damage sperm and increased CYP2E1 enzyme levels in germ cells, even though they were not directly exposure to acrylamide (Katen, Chambers, Nixon, & Roman, 2016).

The involvement of the CYP2E1 enzyme, responsible for the acrylamide metabolism, in germ cell mutagenicity was investigated in studies using knockout CYP2E1 male rats (Ghanayem et al., 2005). The animals were treated with 0, 12.5, 25 or 50 mg acrylamide/kg/day for 5 consecutive days and were mated to untreated females. The number of live and viable fetuses was reduced in females mated with wild-type males while no differences were observed in females mating with knockout mice. Taken together, these results demonstrated that acrylamide-induced germ cell mutations require the formation of the CYP2E1-mediated epoxide metabolite. Thus, polymorphisms in CYP2E1 enzyme may result in different susceptibility degree to acrylamide toxicity (Ghanayem et al., 2005).

The acrylamide effects on the offspring reproductive system was assessed in combination with alcohol in rats treated during the gestational and lactation periods (Şen, Tunali, & Erkan, 2015). The results pointed out that the acrylamide consumption in association with alcohol impaired the testicular spermatogenesis in male offspring, evidenced by the presence of multinucleated giant and degenerative cells, as well atrophic seminiferous tubules, associated with increased in the lipid peroxidation and in the superoxide dismutase activity. Besides that, a decrease in Leydig and Sertoli cells was observed (Şen et al., 2015).

Corroborating these findings evidences of histopathological lesions, as generation of multinucleated and giant cells, vacuolization and numerous apoptotic cells were noticed in seminiferous tubules of animals treated with acrylamide for 5 days (60 mg/kg/day). In addition, the expression of several genes related to testicular functions, apoptosis, cell growth and cell cycle was altered in acrylamide treated group (Yang et al., 2005). A summary of the toxic effects after acrylamide exposure in experimental models is shown in Table 1.

6. Effects on thyroid axis

The acrylamide effects on hypothalamus-pituitary-thyroid (HPT) axis are poorly investigated and the literature is scarce. A cohort study, conducted between 1999 and 2000, examined the association between urinary levels of the acrylamide metabolite (*N*-acetyl-S-propionamide-cysteine) and serum thyroid hormone measurements in teenagers and young adults (793 subjects). Linear regression analysis showed that the increase in urinary metabolite levels was associated with a decrease in thyroxine (T4), especially in women aged between 20 and 30 years old (Lin et al., 2015).

Acute acrylamide exposure (2 mg/kg/day and 15 mg/kg/day, up to 7 days) did not show clinical sign of toxicity or significant difference in the body weight of Fischer 344 female mice treated compared to control group (Khan, Davis, Foley, Friedman, & Hansen, 1999). After 2 days of exposure, the histopathological studies did not present significant alterations in different tissues evaluated. Plasma T4, thyroid stimulating hormone (TSH) and prolactin serum levels, as well as the TSH and prolactin content in pituitary gland revealed no significant changes between control and treated rats (Khan et al., 1999). However, after 7 days of exposure there was a slight dose-dependent increase in plasma T4 level and a small decrease in TSH serum concentration. The morphometric analysis of the thyroid gland showed a significant decrease in the colloidal area and an increase in the follicular cells height of acrylamide treated mice compared to control (Khan et al., 1999).

Studies carried out in male rats showed that acrylamide reduced the

Table 1
Summary of the toxic effects after acrylamide exposure in experimental models.

Effects	LOAEL for the study	Experimental model	Age at beginning of exposure	Exposure duration	Exposure route	Main results	Reference
Reproductive system	5 mg/kg/day	♂ Sprague–Dawley rats	9 week-old	5 days	Oral gavage	↓ serum testosterone level ↓ leydig cell viability ↓ spermatogenesis ↓ genes related to testicular-functions, apoptosis, cellular redox, cell growth, cell cycle, and nucleic acid-binding were up/down-regulated in testes isolated from acrylamide-treated group (60 mg/kg/day)	Yang et al. (2005)
	12,5 mg/kg/day	♂ wild-type and CYP2E1-null mice ♀ B6C3F1 mice	8 week-old	5 days	intraperitoneal injection	induced germ cell mutations in male mice and required CYP2E1-mediated epoxidation of acrylamide	Ghanayem et al. (2005)
	15 mg/kg/day	♂ Long-Evans rats	11 week-old	5 days	Oral gavage	↓ weight gain ↓ mating, fertility, and pregnancy	Tyl, Marr, Myers, Ross, and Friedman (2000)
	25 mg/kg/day	♂ ♀ C57Bl/6J mice	5–30 week-old	5 days	Oral gavage	↓ live fetuses ↓ induced obesity ↓ male fertility ↓ germ cell mutagenicity	Ghanayem, Bai, Kissling, Travlos, and Hoffler (2010)
	25 mg/kg/day	♀ BALB/c mice	Adult	7 days	intraperitoneal injection	↓ maturation of the oocytes ↓ meiotic spindle mass of the oocytes ↓ chromosomal disruption	Aras et al. (2017)
	25 mg/kg/day	♂ albino rats	Adult	10 days	Oral gavage and intraperitoneal injection	degeneration of germ cells, numerous multinucleated giant cells with sloughed seminiferous epithelium, and vacuolation in-between the germ cells	Mustafa (2012)
	10 mg/kg/day	♂ F344 rats	Adult	14 days	in drinking water	↓ serum testosterone - activated the HPG axis - A dose of 50 mg/kg altered histology of Leydig and germ cells	Camacho, Latendresse, Muskhelishvili, Patton, Bowyer, Thomas et al. (2012)
	5 mg/kg/day	♂ Sprague-Dawley rats	3 week-old	28 days	Oral gavage	↑ serum testosterone and FSH ↓ LH - Histopathological lesions and abnormal sperms	Ma et al. (2011)
	20 mg/kg/day	♂ Kunming mice	Adult	28 days	intraperitoneal injection	apoptosis induced by acrylamide is suppressed in a 21.5% fat diet through caspase-3-independent pathway in mice testis	Zhang, Chen, and Huang (2009)
	20 mg/kg/day	♀ Kunming mice	5 week-old	30 days	Oral gavage	↓ body weights, organ weights and the number of corpora lutea; ↓ Serum progesterone; ↑ Nitric oxide synthase activity	Wei et al., 2014.
	10 mg/kg/day	♂ Syrian mice	10 week-old	35 days	in drinking water	↑ serum testosterone levels ↑ sperm count, motility and viability ↓ sperm with abnormal morphology	Pourentezari, Talebi, Abbasi, Khalili, Mangoli, and Anvari (2014)
	10 mg/kg/day	♀ mice	3 week-old	42 days	Oral gavage	↑ oocyte quality ↑ Ovary weights ↑ litter size	Duan et al. (2015)
	10 mg/kg/day	♂ Sprague–Dawley rats	3 week-old	56 days	Oral gavage	↓ epididymal sperm reserves ↑ histopathologic lesions in the testes	Wang et al. (2010)
	10 mg/kg/day	♂ Sprague–Dawley rats	3 week-old	56 days	Oral gavage	↓ weights of the testis and epididymis and the sperm concentration in the cauda of the epididymis ↓ histopathological lesions and the number of Leydig cells around the apoptosis seminiferous tubules	Wang et al. (2007)
	5 mg/kg/day	♂ NMRI mice	8–10 week-old	2 months	Oral gavage	↓ total sperm motility and progressive motility ↓ integrity of the sperm tail membrane (only with 10 mg/kg/day)	Kermani-Alghoraishi, Anvari, Talebi, Amini-Rad, Ghahramani, and Miresmaili (2010)
	14 mg/kg/day	Pregnant *Mus musculus* Balb/c mice and offspring	Adult	from gestation day 6 to postnatal day (PND) 21	Oral gavage	↑ multinuclear giant cells, degenerative cells, atrophic tubules, and maturation-arrested tubules ↓ Leydig, Sertoli, and spermatogenic cell numbers ↓ consumption of AA together with alcohol may induce impairments on testicular spermatogenesis in male offsprings	Şen et al. (2015)
	3 mg/kg/day		12,8 week-old		in drinking water	↑ number of primordial and primary follicles	

(*continued on next page*)

Table 1 (*continued*)

Effects	LOAEL for the study	Experimental model	Age at beginning of exposure	Exposure duration	Exposure route	Main results	Reference
		Pregnant guinea pigs (Himalayan-Guinea Pig)		beginning on gestation day 32 until parturition		↑ defects in the granulosa cell-oocyte interactions ↑ follicular atresia	Hułas-Stasiak et al. (2013)
Thyroid system	2 mg/kg/day	♀ Fischer 344 rats	~3 week-old	2 or 7 days	Oral gavage	↑ T4 ↓ TSH ↓ colloid área of thyroid ↑ follicular cell height	Khan et al. (1999)
	2.5, 10 and 50 mg/kg/day	♂ Fischer 344 rats	Adult (~70 day-old)	14 days	in drinking water	↑ there was no change in the major genes regulating the thyroid axis	Bowyer et al. (2008)
	5 mg/kg/day	♂ Sprague Dawley rats	Adult	56 days	Oral gavage	↑ carcino embryonic antigen (CEA) ↑ malondialdehyde (MDA) ↓ free and total testosterone ↓ T3 and T4 ↑ corticosterone levels	Hamdy et al. (2012)
	21 mg/kg/day	rats	Adult	28 days	Oral gavage	↑ initial nerve terminal argyrophilia was followed by abundant retrograde axon degeneration in white matter tracts of spinal cord, brain stem, and cerebellum	LoPachin et al. (2003)
Neurological	5 mg/Kg/day	Pregnant Wistar rats	Adult	during pregnancy	Oral gavage	- degeneration in neuron structures in fetal brain tissue - hemorrhagic damages; decreased ↓ brain-derived neurotrophic factor levels ↑ malondialdehyde ↑ total oxidant capacity levels; and ↓ reduced glutathione ↑ total antioxidant capacity levels	Erdemli et al. (2016)
	20 mg/Kg/day	♂ Sprague-Dawley rats	6–7 week-old	20 days	Oral gavage	↑ dopamine levels; ↓ 3,4-dihydroxyphenylacetic acid ↓ homovanilic acid - dopamine transporter and vesicular monoamine transporter expression levels in the striatum	Pan et al. (2015)
	50 mg/Kg/day	Wistar albino rats	21 days	5 days	single intraperitoneal injection	↑ dopamine, interferon-g, 8-hydroxyguanosine ↓ serotonin	Zargar et al. (2016)
	25 mg/Kg/day	♂ Wistar albino rats	adult	21 days	Oral gavage	dopamine, noradrenaline. and 5-hydroxytryptamine	Dixit et al. (1981)
	50 mg/Kg/day	Albino male rats	adult	10 days	intraperitoneal injection	↓ brain glutathione content - glutathione-S-transferase inhibition ↑ dopamine receptors ([3H] spiroperidol binding)	Srivastava et al. (1986)
	21 mg/Kg/day	Sprague-Dawley rats	adult	21 days	Oral gavage	↓ vesicular dopamine uptake ↓ KCl-evoked synaptosomal dopamine release	LoPachin et al. (2006)
	10–625 mg/L	Caenorhabditis elegans		48h		- degeneration of dopaminergic neurons - α-synuclein aggregation ↓ locomotor frequency of body bending ↓ head thrashing ↓ pharynx pumping	Li et al. (2016)
	100 ppm	♂ Long Evans rats	70 days old	6 weeks	in the drinking water	↑ 5-hydroxyindoleacetic acid in the striatum, septal area, and thalamus - Sciatic nerves showed histopathological changes characteristic of multi-focal dying-back peripheral nerve degeneration	Rafales et al. (1983)
	10 mg/Kg/day	♂ Fisher 344 rats	8–10 weeks old	20 days	intraperitoneal injection	↑ serotonin in the brain stem ↑ dopamine in the caudate nucleus ↑ 5-hydroxyindole acetic acid (5HIAA) in different regions of the brain	Ali (1983)
	0–1.0 mM	primary astrocytes/ microglia co-culture from Balb/c mice		24–96h		↑ reactive oxygen species ↓ glutathione ↑ 4-hydroxynonenal-adduct and 8-hydroxy-2-deoxyguanosine-adduct	Zhao et al. (2017)
	0.1 and 1 mM	astrocyte cultures from the Fischer 344 rats		7, 11, 15, or 20 days		↑ proliferating cell nuclear antigen (PCNA) protein expression in astrocytes ↑ astrocytic cell proliferation	Aschner et al. (2005)

triiodothyronine (T3) and T4 serum levels and these alterations precede the carcinogenic activity induced by acrylamide on thyroid, testes and adrenal gland (Hamdy, Bakeer, Eskander, & Sayed, 2012). On the contrary, Bowyer et al. (2008) demonstrated that acrylamide did not promote systematic changes in expression of genes related to the HPT axis, suggesting that hormonal dysregulation might not be associated to acrylamide-induced carcinogenesis in Fischer 344 rats.

It is noteworthy that acrylamide and glycidamide are able to form adducts with nucleophilic regions of proteins altering their structure and function. The valine present in the hemoglobin, *i.e.*, covalently binds to acrylamide and glycidamide (FAO/WHO, 2005; Hagmar et al., 2001). According to LoPachin, Gavin, Decaprio, and Barber (2012) acrylamide also presents high reactivity to sulfhydryl groups presented in certain proteins. The tertiary structure of TSH molecule obtained from molecular modeling studies, showed that both α and β subunits are linked by disulfide bonds which could make the TSH molecule susceptible to interaction with acrylamide (Szkudlinski, Fremont, Ronin, & Weintraub, 2002). The post-translational processing of immature TSH involves glycosylation, folding, binding between of α and β subunits and modifications in the addition of sugars. All these steps are important for the folding pattern and the TSH ability to bind to its receptor at the plasma membrane of the thyroid cells (Ortiga-Carvalho, Chiamolera, Pazos-Moura, & Wondisford, 2016). Thus, the interaction between TSH and acrylamide could alter the post-translational processing and consequently the TSH activity.

The acrylamide also exhibits high affinity by amino terminal portion of proteins and the NH group of the histidine ring (Friedman, 2003). Considering that, acrylamide could also interact with MCT8 changing its affinity by T3. Furthermore, the cytochrome P450 enzyme (CYP2E1 enzyme) is moderately expressed in the thyroid cells, leading to the formation of glycidamide, a more reactive metabolite, in the thyroid gland (Bieche et al., 2007).

Further studies are needed to clarify the better understand the consequences to acrylamide exposure and to characterize it as an endocrine disruptor using international screening protocols for EDCs. A summary of the toxic effects after acrylamide exposure in experimental models is shown in Table 1.

7. Neurotoxic effects

The nervous system is an important target for the toxic acrylamide effects. Degeneration of peripheral nerve and nerve terminals in some brain areas (cerebral cortex, hypothalamus, and hippocampus) related to the memory, learning and cognitive functions was observed after repeated exposures to acrylamide (FAO/WHO, 2005).

A study conducted with two different doses of acrylamide in rats (50 or 21 mg/kg/day) showed a progressive degeneration of nerve terminals in all central nervous system (CNS) regions and neurotoxic symptoms as ataxia and muscle paresis (LoPachin, Balaban, & Ross, 2003). The acrylamide seems to act directly on the nerve end sites, causing synaptic dysfunction and degeneration. Damages to the peripheral and CNS result in motor, sensory and autonomic deficits (LoPachin, 2004). Moreover, studies conducted by Erdemli, Turkoz, Altinoz, Elibol, and Dogan (2016) have shown that the acrylamide treatment to mothers causes degeneration in the neuronal structures in fetal brain tissue, hemorrhagic damage and reduction on brain-derived neurotrophic factors levels. *In vitro* studies pointed out that acrylamide reduces the proliferation and differentiation of progenitor neural cells, as well as, the expression of neural and astrocytes biomarkers (Attoff, Kertika, Lundqvist, Oredsson, & Forsby, 2016). Though the detailed pathway is not yet clear, there are three main hypotheses related to the mechanism of neurotoxicity triggered by acrylamide: a) the inhibition of kinesin-based fast axonal transport; b) the alteration of neurotransmitter levels and; c) the direct inhibition of neurotransmission (Erkekoglu & Baydar, 2014).

Several studies pointed out for a correlation between acrylamide-induced neurotoxicity and dysfunctions of the dopaminergic system, even though the results were discrepant. Reduction in the dopamine, noradrenaline and 5-hydroxytryptamine levels after acrylamide treatment were reported by Dixit, Husain, Mukhtar, and Seth (1981). In contrast, Pan et al. (2015) demonstrated that the acrylamide administration led to an increase in the dopamine levels, as well as changes in dopamine transport and decrease on expression of genes related to the acrylamide metabolism in dopaminergic neurons. In this sense, Zargar, Siddiqi, Ansar, Alsulaimani, and El Ansary (2016) also showed a significant increase in dopamine, interferon-γ and 8-hydroxyguanosine with a concomitant decrease in serotonin in rats' brains after acrylamide administration of 50 mg/kg/day. Srivastava, Sabri, Agrawal, and Seth (1986) also observed that acrylamide reduced glutathione levels and increased dopamine receptors ([3H] spiroperidol binding) in a concentration-dependent manner.

Sub-acute exposure of acrylamide results in functional damage of proteins and synaptic vesicles, an additional mechanism involved in the acrylamide neurotoxicity (Zhao, Lewis Wang, Hu, Chen, & Chan, 2017). Moreover, the dopamine uptake was shown to be inhibited by acrylamide in rat striatal synaptic vesicles, disrupting the dopamine storage, which might mediate a defective presynaptic release (LoPachin, Barber, He, & Das, 2006).

Li et al. (2016) also demonstrated acrylamide-induced degeneration of dopaminergic neurons as well as α-synuclein aggregation, which may be related to induction of parkinsonian pathology. Rafales, Lasley, Greenland, and Mandybur (1983) showed that the chronic exposure (6 months) to acrylamide (100 ppm) increased the psychomotor stimulation in response to D-amphetamine in male rats and this effect may be related to changes in a serotonergic inhibitory system. Changes in the dopamine, serotonin and 5-hydroxyindolacetic acid levels in different regions of the brain were previously described (Ali, 1983), however, a significant increase in serotonin levels in the brainstem led the authors to suggest that the neurotoxicity of acrylamide may be related to changes in the serotoninergic system, as well.

Furthermore, study performed in primary astrocyte model showed a dose-dependent neurotoxicity induced by acrylamide. Oxidative stress was also induced by increased reactive oxygen species and decreased GSH levels (Zhao et al., 2017). In contrast, Aschner, Wu, and Friedman (2005) have described that acrylamide promotes the proliferation of astrocytic cells in the central nervous system. Structural changes in the development of the cortical layers of the cerebellum in newborn rats was shown to be induced by acrylamide and these effects were prevented by vitamin C, acting as an antioxidant (Dortaj et al., 2018).

Although these effects have been described, the lesion extension in CNS due to acrylamide exposure is still poorly investigated. Taken together, the studies suggest that the NOAEL should be around 0.2 and 0.5 mg/kg/day (FAO/WHO, 2005). A summary of the toxic effects after acrylamide exposure in experimental models is shown in Table 1.

8. Final considerations

From the literature review, it is notable that the main focus of *in vivo* research is the acrylamide toxic effects. However, it is known that some effects of EDCs are triggered in lower doses altering the physiological hormonal balance, without clinical signs of toxicity. Another important aspect to be considered is that most of the studies evaluated the acrylamide effects in animal adult phase and usually for short periods of treatment. There are very few studies investigating the effects of acrylamide during the embryonic and/or pre-puberty periods, which are considered to be more susceptible to endocrine disruption.

Among the studies evaluating the effects acrylamide on reproductive system, only four were performed with onset of acrylamide exposure to young animals (21 days old) (Duan et al., 2015; Ma et al., 2011; Wang, Ge, Zhou, Wang, & Shi, 2007; Wang et al., 2010). Ma et al. (2011) highlighted the importance of performing toxicological studies during embryonic and pre-puberty stages rather than only in adult

animals considering the harmful effects at these early stages of life.

The minimum dose used in experiments performed during the development period was 5 mg acrylamide/kg/day, followed by increasing doses as 10, 15, 30 and 50 mg/kg/day that could trigger some clinical effect (Duan et al., 2015; Ma et al., 2011; Wang et al., 2007; Hao Wang et al., 2010). The data presented in Table 1 shows that the range of doses of acrylamide evaluated in the reproductive studies was about 2 and 60 mg/kg/day, which were similar or higher than the dose considered by NOEL (2 mg/kg/day) regarding the effects in the reproductive system (FAO/WHO, 2005).

The Endocrine Disrupter Screening and Testing Advisory Committee (EDSTAC) proposed a protocol for the identification of EDCs taking into account the period of exposure, the animals age and doses tested (Stoker et al., 2000). However, until the present date, there is no study for acrylamide effects following the mentioned protocol.

Regarding the acrylamide effects on thyroid system, a single study was carried out at a young female rats subjected to acute acrylamide exposure (2 and 15 mg/kg/day) for 2 or 7 days (Khan et al., 1999). In addition, two other studies have been carried out on adult male rats testing higher doses of acrylamide (2.5, 5, 10 and 15 mg/kg/day) (Bowyer et al., 2008; Hamdy et al., 2012). Although the study performed by Bowyer et al. did not show relevant alterations on genes related to the regulation of HPT axis, other authors have shown that the thyroid morphology and the T4 and T3 blood levels were altered after the acrylamide exposure, emphasizing the acrylamide effects on thyroid system (Hamdy et al., 2012; Khan et al., 1999). Considering that these are the only studies evaluating the relationship between thyroid hormonal balance and acrylamide, it is clear that further and deep evaluation from the endocrine disruption perspective is extremely.

It is worth mentioning that some experiments were performed using intraperitoneal administration of acrylamide or it was added to the drinking water for the animals. Such studies present important limitations since intraperitoneal route does not represent a common exposure pathway for the acrylamide in humans. On the contrary, the addition of acrylamide in drinking water could be comparable to the human exposure pathway; however, the amount of water ingested by each animal could be variable and is usually measured by consumption of ingested water per box/cage. Thus, the results would be analyzed considering an estimative of the daily dose per kg of the animal, which could impair the dose-response analysis as well as, the establishment of safe doses. The same bias is also observed in studies in which acrylamide is added to the animal feed and the dose is expressed in mg/kg diet as proposed by Alkarim, ElAssouli, Ali, Ayuob, and ElAssouli (2015), Raju et al. (2016).

9. Conclusion

It is important to reinforce that EDCs may not follow the classic toxicology dose–response curve pattern. As observed for endogenous hormones, which physiological levels are extremely low (nanomolar – picomolar), some EDCs may induce significant alterations only when administered or exposure to low doses (Schmutzler et al., 2007). According to Vandenberg et al. (2012), certain substances may present monotonic (linear and non-linear) and non-monotonic dose-response curves. Changes in the slope of the curve resulting in a U-shaped curve (maximal responses at low and high doses) or inverted U (maximal responses at intermediate doses) are also possible. In some complicated cases, there are multiple points along the curve where the slope can invert the signal. Thus, it is difficult to establish which dose-response pattern can be described for acrylamide, since it may vary according to the tissue/cell evaluated.

The dynamics of receptor occupancy and its relation to the hormone concentration is quite complex. Previous studies have shown that the relation between receptor occupancy and hormone concentration (ligand) is not linear and the saturation of response occurs under the dissociation constant values for the receptor-ligand binding, while the saturation of the receptors is observed only at higher concentrations of hormone. Thus, there is a non-linear relationship between the number of bound receptors and the biological effect (Vandenberg et al., 2012; Welshons et al., 2003), which make the understanding regarding the EDCs effects and pathways triggered, as acrylamide *i.e.*, a real challenge but extremely necessary, in attempt to establish the safe levels of consumption and exposure.

Considering the higher consumption of foods rich in acrylamide compounds and its potential effect on different endocrine systems, the necessity of further studies becomes evident to clarify the effects, molecular mechanisms of action and the consequences for the human healthy.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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