DOI: 10.5281/zenodo.33495

Food Packaging Forum

Dossier – Bisphenol A

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1 Physical and chemical properties

Bisphenol A (**BPA**; CAS 80-05-7; IUPAC name: 4,4'-(propane-2,2-diyl)diphenol) is an organic compound with two hydroxyphenyl groups and has the chemical formula $C_{15}H_{16}O_2$ (**1**; Figure 1). At room temperature, it is a white solid that is described to have a mild phenolic odor [2]. BPA is well soluble in acetic acid, aqueous alkaline solutions and organic solvents such as acetone, benzene and ether [2, 4], but only poorly soluble in water (120-300 mg/L at 25°C) [7]. Its octanol/water partition coefficient (K_{OW}) is 3.32 [9].

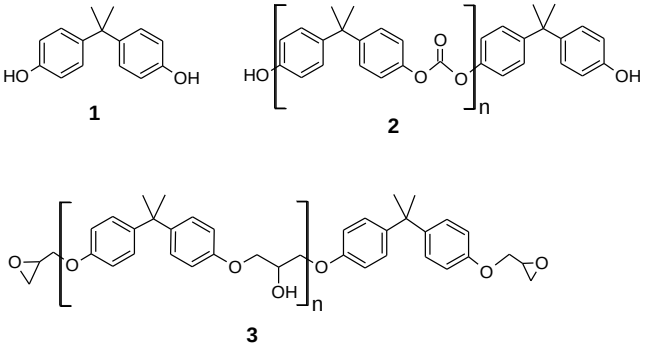

Figure 1. Chemical structure of bisphenol A (BPA) **1**, polycarbonate **2** and an epoxy resin composed of BPA and epichlorohydrin **3**.

2 Production and use

Bisphenol A is synthesized by condensation of one molecule of acetone with two molecules of phenol in the presence of hydrogen chloride or cross-linked polystyrenes that act as catalysts [11]. Impurities of the phenol-acetone condensation reaction are the tri- or mono-hydroxy by-products [5]. BPA is mainly used to produce polycarbonate and epoxy resins (Table 1). Furthermore, BPA is applied as color developer in thermal papers and as building block in the synthesis of the flame retardant tetrabromobisphenol A. Besides many other applications, both polycarbonate and epoxy resins are widely used as food packaging materials. Re-usable food containers and bottles are often made of polycarbonate because this material is shatter-proof, durable, light and transparent. Epoxy resins are used as can coatings, and for avoiding the contact between steel or aluminum and food. They prevent corrosion of the metal can by food and protect the product`s taste at the same time. Furthermore, epoxy resins can be found in food and menu trays, and the linings of caps, closures and crown corks.

The main polycarbonate material is produced by a reaction of BPA and phosgene yielding a polymer with the structure shown in Figure 1 (**2**). Most epoxy resins are produced by a condensation reaction between BPA and epichlorohydrin (Figure 1, **3**) and are further stabilized and/or modified by different cross-linking reactions. Thus, a wide variety of different BPA-based epoxy resins is available on the market and more than 95% of all food can coatings belong to this group [13].

3 Market data

During the 80s, the world production capacity of bisphenol A was about 1 million tons per year [11]. Estimates from the first decade of this century showed that the global production capacities were always (far) higher than 2 million tons per year with a maximum of 5.2 million tons in 2005 (Table 2). It has to be mentioned that these data originate from different sources and thus any comparison or even extrapolation should be done very carefully. Between 2002 and 2004, US American, European and Asian companies produced approximately 30, 30 and 40% of global BPA, respectively [8, 14, 15].

Table 2. Global production capacity of BPA. Note that the data come from different sources.

Year	Global capacity (million tons/year)	Reference
80s	≈ 1	[11]
1990-98	> 1.0	[16]*
2002	2.9	[8]*
2003	3.0-3.4	[17]**, [15]***
2004	3.7	[14]*
2005	5.2	[14]***
2006	3.7-3.8	[18]**
2009	2.2	[19]**

* Citations were adopted from the bisphenol A factsheet obtained from the peer-reviewed National Library of Medicine HSDB Database [1].
** Data obtained from web pages with unconfirmed information.
*** Citations were adopted from the Bisphenol A Market Analysis Report [12].

Table 1. US Consumption pattern for BPA

Year	1973	1984	1986	1995/6	2000	2002	2004
Reference	[1]	[1]	[3]*	[5]**	[6]*	[8]*	[10]**
Polycarbonate resins	53%	52%	57%	55%	68%	65%	73%
Epoxy resins	31%	41%	36%	40%	24%	22%	21%
Tetrabromobisphenol A		2%				2%	
Miscellaneous	16%	5%	7%	5%	8%	2%	6%

* Citations were adopted from the Bisphenol A factsheet obtained from the peer-reviewed National Library of Medicine HSDB Database [1].
** Citations were adopted from the Bisphenol A Market Analysis Report [12].

4 Historical dates

- In 1891, BPA was synthesized by the Russian chemist Alexander Pavlovich Dianin.
- Already in 1934 and 1936, Dodds and Lawson described that BPA and a range of related compounds exhibit estrogenic activity in ovariectomized rats [20, 21].
- Twenty years later, BPA was used as monomer in the production of polycarbonate and in consequence it entered the list of the most important industrial chemicals [22].
- Standard toxicology tests of BPA were performed in the 80s and a Reference Dose for Chronic Oral Exposure (RfD) of 0.05 mg/kg body weight/day was set according to the results of these tests [23].
- In the beginning of the nineties, endocrinologists from Stanford University identified a compound with estrogenic properties that contaminated their assays: BPA was leaching from polycarbonate flasks during autoclaving and bound to the mammalian estrogen receptor [24]. This study was a starting point of many more that describe various estrogenic and endocrine disrupting effects of BPA. – In 1997, adverse health effects of low-dose BPA exposure on laboratory animals were reported for the first time. Colerangle and Roy found out that BPA induces a proliferative effect in breast tissue at low doses [25]. Nagel et al. described enlarged prostates in the male offspring of mice that were fed low doses of BPA during pregnancy [26].
- April 2002: A total of 47 peer-reviewed studies report on low-dose effects of BPA in all species [27].
- In 2004, Gray et al. published an industry-funded report that questions the existence of adverse health effects of BPA. In this report, 7 of 9 industry-funded and 12 of 38 government-funded studies were reviewed [28].
- In 2004, 94 out of 115 publications, which were obtained from PubMed searches, reported low-dose estrogenic effects of BPA [27]. vom Saal and Hughes correlated the source of funding with the outcome of the studies and showed that the results were highly dependent on the source of funding.
- Fall 2006: A conference was organized by the National Institute of Environmental Health Sciences (NIEHS) to investigate BPA's safety. As a result, 38 scientists who are experts in this field published the Chapel Hill Consensus Statement [29] as well as five review articles [30-34]. During the conference the experts addressed five major concerns about BPA and finally they agreed on scientific data with high confidence and on data requiring further confirmation.
- In 2008, the Canadian government published a draft screening assessment, in which BPA was considered as a possible danger to human life or health. Two years later, the Canadian government restricts the use of BPA in baby bottles (Hazardous Products Act, Bisphenol A).
- 2009: The NIEHS launched a multipronged research program to fill data gaps and resolve controversies about the design and interpretation of BPA toxicity studies [35]. Between January 2010 and December 2012 more than 100 papers were published that were either funded by the NIEHS or written by intramural researchers.
- 2010: Over 30 experts attended a meeting that was organized by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (FAO) (WHO) to review the toxicological and health aspects of BPA. A final report and 15 expert papers were published as a result. These publications summarize the state of knowledge and also highlight controversies and data gaps [36].
- The European Commission and the FDA restrict the use of BPA in baby bottles in 2011 (EU 321/211) and 2012 [37], respectively.
- In 2012, the European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) for an updated Scientific Opinion on the risk assessment of dietary BPA. The Draft Scientific Opinion on the risks to public health related to the presence of BPA in food stuffs was published in two parts in July 2013 and January 2014, respectively [38, 39].

5 Current risk assessment provokes a controversial scientific debate

The risk assessments of BPA by EFSA and the FDA have been discussed highly controversially during the last years. The risk assessments provided by these two authorities [40, 41] were based on toxicity tests in experimental animals, which were performed according to Good Laboratory Practice (GLP) guidelines. Tyl et al. performed two multigenerational reproduction studies in rats [42] and one multigenerational reproduction study in mice [43], which were both identified as pivotal in risk assessment by EFSA and FDA. Both studies showed non-specific toxicity and identified a Lowest Observed Adverse Effect Level (LOAEL) of 50 mg/kg body weight/day and a No Observed Adverse Effect Level (NOAEL) of 5 mg/kg body weight/day. The Tolerable Daily Intake (TDI) of 0.05 mg/kg body weight/day was calculated on the basis of these numbers applying a safety factor of 100.

Already in 2005, vom Saal and Hughes published an article about the needs for a new risk assessment due to low-dose estrogenic effects of BPA observed in 94 studies [27]. In 2009, Myers et al. strongly criticize the decisions of FDA and EFSA to declare BPA safe at current exposure levels [44]. This paper was the starting point of a highly-controversial debate regarding BPA`s risk assessment. The topics of the debate include the quality of the applied test systems and investigated endpoints, the source of funding, the quality standards, misinterpreted and/or neglected results, methodological flaws, and many more [45-51]. This scientific dispute was also continued in the public press, where it got an even more political dimension [52].

6 Current regulations

6.1 European Union

BPA is an authorized food contact material according to Regulation EU 10/2011. Its use as monomer for the production of plastics is approved. BPA has a Specific Migration Limit (SML) of 0.6 mg/kg food. Since 2011, the use of BPA in plastic feeding infant bottles is restricted (EU 321/211).

In 2002, the European Commission's Scientific Committee on Food (SCF) issued an opinion on BPA and set a temporary TDI of 0.01 mg/kg body weight/day. The EFSA re-evaluated BPA`s safety in 2006 [40] and increased the TDI to 0.05 mg/kg body weight/day by reducing the uncertainty factor from 500 to 100 due to new scientific evidence. Until 2010, several updates of this Scientific Opinion were published, but no changes in key figures occurred [53]. Just recently, EFSA proposed to reduce the TDI by a factor 10 from 0.05 to 0.005 mg/kg body weight/day [39]. Awaiting the findings of research carried out by the U.S. National Toxicology Program (NTP), the National Institute of Environmental Health Sciences (NIEHS) and the FDA, the newly proposed TDI should be set on a temporary basis. These results are expected earliest in 2015 [54].

The German Federal Environmental Agency (UBA) favors precautionary action and restrictions on certain products that contain BPA, because they see causes for concern [55]. The French Agency

for Food, Environmental and Occupational Health and Safety (ANSES) published two reports on the health effects and the uses of BPA [56], which were followed by a proposal to the ECHA that demands a more stringent classification of BPA by the EU due to its reprotoxic effects. In October 2013, the French Senate revised a new law that is going to ban BPA from food contact materials by July 2015 (Loi n° 2012-1442). The Swiss Federal Office for Public Health does not see any risk for the consumer by BPA released from food packaging [57].

6.2 United States

BPA was originally approved under the FDA`s food additive regulations from the 1960s. In 2008, a review of BPA was completed by the NTP Center (part of the National Institute of Health). The NTP expressed "some concern for effects on the brain, behavior, and prostate gland in fetuses, infants and children at current human exposure to bisphenol A" and "minimal concern for effects on the mammary gland and an earlier age for puberty for females in fetuses, infants, and children at current exposures to bisphenol A" [58]. In the same year, the FDA published a draft assessment of BPA [41], which contradicts the results of the NTP report: "…the results of FDA's assessment indicate that the data reviewed on endpoints highlighted as of potential concern in recent reports, such as developmental effects on the prostate gland and developmental neural and behavioral toxicity, are insufficient to provide a basis to alter the NOAEL used to calculate the margin of safety." In the following years, the FDA continued to study BPA`s effects on human health by various studies. Since July 2012, the use of BPA in baby bottles is restricted by the FDA [37]. FDA has an ongoing collaboration with NIEHS and NTP on the safety assessment of BPA [54, 59].

7 Molecular mechanisms of BPA action

BPA is a xenoestrogen that does not contain the typical steroid building blocks that characterize steroid hormones, but nevertheless it mimics the action of estrogens. Furthermore, it is an endocrine disrupting compound in the broad sense, because it disturbs also non-estrogenic pathways and causes biological effects at low-dose concentrations. More recently, several studies were published on BPA that describe its epigenetic modes of action. The multitude of different mechanisms that are caused by BPA was recently clearly reviewed by Wolstenholme et al. [60].

7.1 BPA as estrogen receptor agonist

Originally, BPA was thought to primarily disrupt the classic estrogen-triggered pathway that controls strogen-responsive gene expression. BPA binds to the classical α- and β-estrogen receptors in the nucleus (ER-α and ER-β), but with at least 1000-fold lower binding affinities than the human estrogen estradiol [61]. Furthermore, it activates membrane-bound estrogen receptors (mER and GPR30) and the estrogen-related receptor gamma (ERR-γ) at very low doses. These non-classical estrogen triggered pathways that are activated by BPA were recently reviewed in detail [62].

7.2 BPA effects on the androgen receptor

BPA acts as androgen receptor (AR) antagonist and affects its activation and function by competitive inhibition, changing the nuclear localization of AR and subsequent trans-activation [60].

7.3 Further endocrine-related mechanisms of BPA

BPA inhibits aromatase activity in human cell lines which results in reduced testosterone and estradiol synthesis levels. Furthermore, it interferes with the metabolism of xenobiotics by altering the expression of the aryl hydrocarbon receptor (Ahr), the Ahr-nuclear translocator and the Ahr repressor. BPA also influences thyroid hormone levels by binding to the thyroid hormone receptor [60].

7.4 Epigenetic effects of BPA

BPA can reduce the methylation of specific DNA (CpG) sites [63], which is generally associated with reduced gene activity. Future research has to find out whether BPA also induces methylation of non-CpG regions, which was recently observed in human stem cells and might up-regulate gene expression in developing systems [64].

7.5 Combined effects

BPA has several possible modes of action, which are all dependent on the cell type and time of development. Thus, the single effects can provoke different answers depending on the time of exposure. Furthermore, the effects can be enhanced, because BPA acts at multiple levels such as methylation of DNA, hormone signaling and enzyme activity.

8 Physiological effects of BPA

8.1 *In vitro* models

In 2007, a comprehensive review was published by Wetherill et al. [34] as a result of the workshop on BPA held in Chapel Hill in November 2006. This paper lists 61 *in vitro* studies that investigated the low-dose effects of BPA on adipose, bone, breast cancer, embryonic/developmental, endothelium, female and male reproductive tissue, immune system, liver, the nervous system, pancreatic and pituitary models.

8.2 *In vivo* models

One further review that was published in 2007 as result of the same workshop summarizes the effects of BPA in 115 non-aquatic animal models [32]. Only studies that used BPA concentrations below the formerly observed NOAEL of 50 mg/kg body weight/day were considered. The list of observed effects is long and includes changes in brain physiology, brain structure, behavior, sex differences in the brain, puberty in females, the mammary gland, uterus and vagina, ovary oocytes and female fertility, metabolism and the immune system. A report by the European Environment Agency [65] and a book chapter by Allard and Colaiácovo [66] summarized also more recent mammalian studies on BPA. These added further *in vivo* effects such as carcinogenesis, male reproduction, thyroid function and adipogenesis to the existing list.

8.3 Clinical health effects

The number of publications that describes correlations between BPA concentrations and human diseases is steadily increasing. These diseases include diabetes, cardiovascular disease and altered liver enzymes [67, 68]. Furthermore, miscarriages, premature deliveries and unsuccessful *in-vitro* fertilizations were associated with high BPA levels in women [69-71]. In men, semen quality and sperm DNA damage were correlated with increased BPA concentrations [72, 73]. First evidence is given that increased hyperactivity and aggression in 2-year-old girls is correlated with elevated BPA levels [74]. In 2012 and 2013, epidemiological studies linked BPA concentrations with altered thyroid function, metabolic syndrome, obesity, hypertension,

peripheral arterial disease and coronary artery stenosis [75-79]. Most of these results were obtained from cross-sectional study and have to be confirmed by further comprehensive investigations (longitudinal studies). In general, this type of epidemiological studies is difficult to conduct, because the time of exposure often does not coincide with the time when the effects can be detected. For example, exposure of the mother during pregnancy may to be related in certain cases to health effects in the adult offspring.

9 Conclusions from the results of mechanistic, physiological and epidemiological studies

- The scientific community is confident that BPA acts as endocrine disrupting chemical.
- BPA binds to several hormone receptors such as the classical estrogen, androgen and thyroid receptors and several more.
- BPA exhibits non-monotonic dose response curves and acts at low doses that are physiologically relevant. BPA affinity for the estrogen receptors is higher than for the androgen and thyroid hormone receptors; thus BPA can induce completely different effects at different doses.
- BPA alters the epigenetics of animals. The effects are proven, but further research is needed to fully understand the underlying mechanisms.
- BPA effects are strongly dependent on the life stage and the tissue they are targeting. Windows of increased sensitivity especially include the prenatal, neonatal and (pre)pubertal life stage. These windows of increased sensitivity depend upon the time at which specific organs or tissues develop. Time of exposure often does not coincide with the time, when effects can be detected. Often these effects are irreversible.
- Negative health effects of BPA can be explained on different levels as has been done for mammary cancer causation [80].
- Low exposure of adults to BPA has effects on the neurobehavior and the reproduction.
- BPA exposure during the windows with increased sensitivity surely affects the male and female reproductive systems, the thyroid health, the brain and behavior and the metabolism. Epidemiologic studies suggest a link between BPA levels and cardiovascular diseases and metabolic syndrome.
- A fairly new research topic is the association between BPA and obesity [81] indicating that BPA is an important risk factor.

10 Exposure, migration and biomonitoring

BPA that originates from canned food is generally the predominant source of uptake in teenagers and adults [82]. Most cans, and also the jars and lids of glass containers, are coated with epoxy resins to prevent contact between the metal walls of the can and the food. The release of free BPA, which did not polymerize during production of the coating, is dependent on the food, the sterilization process and the storage conditions. High amounts of non-bound BPA are released into the food during the sterilization process. Lower sterilization temperatures retain BPA in the coating, but the residual BPA generally migrates into the food during storage. The concentrations in canned food and beverages were measured worldwide in the last years and vary enormously [82]. Reasons of this variation can be the general composition and application of the coating and the combination of different coatings with a certain food type that influences migration. BPA reached concentrations up to 730 and 840 ng/g food in Japan and the US, respectively, but other samples from around the world were below 1 ng/g food. Beverages were not contaminated in such an extent: the highest concentrations were measured in Belgian drinks (8 ng/mL).

Food containers made from polycarbonate are a further source of food contamination with BPA. Similarly to epoxy resins, non-bound BPA can migrate from polycarbonate food containers, but also hydrolysis/aminolysis of polycarbonate was reported [83]. Especially the use of polycarbonate baby bottles was assumed to be an important uptake pathway in infants [84]. The calculated uptake levels (0.8 μg/kg body weight/day) are below the tolerable daily intake (50 μg/kg body weight/day) set by the European Commission, but they are similar to concentrations that cause low-dose health effects in rodents. Since the ban of polycarbonate baby bottles in the US, Canada and the European Union, this exposure scenario can mainly be ruled out in these countries, but it is still relevant in all other parts of the world.

In 2005, 95% of a representative US American population had detectable amounts of BPA in the urine [85]. BPA was also measured in 93% of healthy infants without known exposure to BPA [86]. These observations indicate that exposure to BPA cannot be avoided in highly-industrialized countries. In 2007, a comprehensive review summarized BPA concentrations in human body fluids [33]. Commonly, total BPA concentrations in urine and serum were reported to be in the low μg/L range. A recent publication compared urinary BPA concentrations in the US and Canada: The mean concentrations were 1.7-2.7 ng/mL and 3.1-4.2 mg/mL (depending on the subpopulation) for Canadians and US Americans, respectively [87].

BPA was also found in fetal tissue, which indicates that it passes the placenta, and in breast milk.

Since 2007 many more studies were published that report new biomonitoring data and could be added to the previously mentioned lists published by Vandenberg et al [33]. A comprehensive review study is currently being prepared by NIEHS grantees and will be published mid-2013.

It should be mentioned that biomonitoring studies often treat urine and plasma samples with the enzyme glucuronidase to release BPA from its conjugated form [87] (for more information see Metabolism and biodegradation). More advanced studies analyze conjugated and free BPA separately. Not all studies that measure BPA in human urine report the creatinine-adjusted concentrations, but only the direct measured values.

11 Metabolism and biodegradation

BPA can be metabolized and excreted via two different routes in humans and other primates. Both metabolites are believed to be biologically inactive. BPA is easily absorbed by the gut wall and glucuronidated in the liver cells. The metabolite, glucuronidated BPA, is measured in human plasma after BPA exposure and excreted in the urine [88]. This mechanism seems to be the major path of excretion in adults [89], but might be reverted by β-glucuronidase-catalyzed hydrolysis [90]. Sulfation by phenol-sulfotransferases in liver cells is one further mechanism of chemoprevention, because BPA is taken up by the cells, sulfated and then actively transported out of the cell. This mechanism prevents re-uptake by liver cells, makes BPA more water soluble and might prevent binding to estrogen receptors. On the other hand, experimental evidence suggests that only sulfated BPA might specifically enter breast cancer cells via the membrane-bound estrone sulfatase that mediates BPA`s desulfation and allows its re-uptake [91]. Therefore, sulfation may lead to estrogenic action of BPA in specifically-targeted cells. The glucuronidation and sulfation systems of neonates are immature, which might lead to higher levels of free BPA in this sensitive group [90].

The difficulties in transferring data from animal models to humans were discussed in a review by Ginsberg and Rice [89], because rodents have other excretion mechanisms that lead to higher levels of free BPA in the blood. Furthermore, the authors focus on the potential adverse effects of free BPA that can be influenced by local deconjugation mechanisms. Thus, they recommend optimized physiologically-based toxicokinetic models to refine the human risk assessment. In 2011, Fisher et al. published a study that helps to predict BPA levels in adult humans on the basis of adult monkey models [92]. The authors also discuss the methodological difficulties in detecting the concentrations of free BPA in human serum and urine and refer to two original papers with inconsistent results [93, 94]. In 2013, Patterson et al. provide evidence that conjugated BPA is selectively deconjugated in the placenta or fetus of rhesus monkeys [95]. Gayrad et al. showed that the way of feeding test animals with BPA strongly influenced free BPA levels in the blood of the animals: when BPA was administered sublingually to dogs, the free BPA levels in the blood were much higher than after BPA administration by gavage (placing a tube into the throat and feeding directly into the stomach) [96]. It is generally accepted that toxicokinetics vary with route of administration, dose, age and even gender, but the presence of free BPA in humans is still subject of controversy. This discussion shows again the strong debates that make BPA research and its risk assessment extremely challenging.

Only few studies report on the degradation (not the excretion) of BPA in humans, but this topic could also be of great concern. Yoshihara et al. incubated BPA with certain fractions of human, monkey and rodent livers and identified a metabolite, 4-methyl-2,4-bis(*p*-hydroxyphenyl)pent-1-ene (MBP), that exhibited higher estrogenic activity than BPA *in vitro* and *in vivo* [97-99]. At the moment no biomonitoring data exist on the presence of MBP in humans.

Although free BPA is mineralized aerobically and anaerobically by various microbial strains [100, 101], it was found in several environmental samples such as air and dust samples, in landfill leachates and surface waters [33]. This is probably due to the steady supply of BPA containing products resulting in a continuous pollution.

Abbreviations

AR	Androgen Receptor
Ahr	Aryl Hydrocarbon Receptor
BPA	Bisphenol A
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
ER	Estrogen Receptor
LOAEL	Lowest Observed Adverse Effect Level
MBP	4-Methyl-2,4-bis(*p*-hydroxyphenyl)pent-1-ene
mER	Membrane Estrogen Receptor
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
SCF	European Commission's Scientific Committee on Food
SML	Specific Migration Limit
RfD	Reference Dose for Chronic Oral Exposure
TDI	Tolerable Daily Intake
TR	Thyroid Receptor
UBA	German Federal Environmental Agency

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