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Survey and risk assessment of developers in thermal paper

Survey of chemical substances in consumer products No. 178

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1. Preface

This report provides a description of results of a survey and a screening of substances in thermal paper, migration from thermal paper and the potential risk in one specific exposure scenario for three different applications of thermal paper with each of their different developer. The study was carried out during the period from June to November 2018 for the Danish Environmental Protection Agency by Danish Technological Institute with DHI as sub-contractor for hazard assessment, exposure scenarios and risk assessment.

In December 2016, the European Commission decided to restrict the usage of the developer bisphenol A (BPA) in thermal paper to max. 0.02 weight percentage; a restriction that comes into force in January 2020. The aim of this survey is, thus, to assess the development of developer usage and to collect information on which alternative developers are in use in thermal paper on the Danish market, the contents and migration of developers from selected applications of thermal paper as well as risk assessment of developers in these applications.

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2. Summary

Today, thermal paper is used for a variety of purposes, e.g. point-of-sales receipts, parking tickets, labels, bank or ATM receipts as well as tickets for public transportation and flight boarding cards. Heat is applied to develop texts or images on paper. To ensure that this is possible, the paper contains a developer, which, among others, may be bisphenol A (BPA). BPA is classified as a reproductive toxicant category 1B, H360F: “May damage fertility”, and EU has adopted restrictions on the content of BPA in thermal paper of 0.02 weight% from January 2020, which is the reason why alternatives to developers in thermal paper are in demand.

For this reason, the developers on the Danish market have been mapped out, a range of products have been included in a screening analysis of content and migration, and realistic worst-case exposure scenarios and risk assessments have been assessed for three different developers in each of their own scenarios. The results of this survey are described in this report.

2.1 Survey and introductory hazard assessment

The survey of developers in thermal paper on the Danish market has been carried out via relevant scientific literature, by consulting manufacturers for accessible knowledge as well as through interviews with Danish companies in the value chain, i.e. converters, importers, distributors/dealers of thermal paper, and consumers of thermal paper.

The survey indicates that BPA, bisphenol S (BPS) and Pergafast 201 are the most widely used developers in thermal paper on the Danish market, while D-8 is also possibly in use. This generally corresponds to available information about the European market; however, there are significant differences in the rate of occurrence of thermal paper for each developer between countries. The application of BPA as developer in thermal paper has decreased both in Denmark and Europe. At the same time, the usage of alternatives has also increased. This may be connected to the active stance towards the problem of BPA among users of thermal paper, where many users will, thus, choose products with phenol- or BPA-free developers. However, there is still a group, often smaller companies, who use the cheapest product, i.e. typically a BPA-containing thermal paper. BPA contents in thermal paper are generally found in approx. 1 weight% with examples from literature of 0.5-3 weight%, and the contents of the alternative BPS, Pergafast 201 and D-8 are found in the same size scale. Technically, the usage of BPS or other identified alternative developers in thermal paper have no disadvantages, since the performance is the same or even better than that of thermal paper with BPA.

TABLE: Overview of developers in thermal paper.

Developer	Type
Bisphenol A (BPA)	Bisphenol
Bisphenol S (BPS)	Bisphenol
BPS-MAE	Bisphenol
TGSA	Bisphenol
D-90	Bisphenol
D-8	Phenol
Pergafast 201	Phenol-free
UU	Phenol-free

The sales of thermal paper are slightly increasing in the EU, and according to the largest part of the companies in the market, the sales are not expected to decrease in the future. It is also expected that the usage of thermal paper will develop towards, among others, a wider range of applications within logistics (packaging labels, etc.), while point-of-sales receipts and tickets will be replaced by electronic receipts to a greater extent. The difference in price between the different types of thermal paper, i.e. with BPA, BPS and phenol-free developers, has been significantly reduced. In 2011, BPS-containing and phenol-free thermal papers were approximately two and five times more expensive than BPA-containing thermal paper. Currently, the price of a BPS-containing thermal paper corresponds to or is slightly higher than a BPA-containing thermal paper, and phenol-free thermal paper costs 16-18% more than a BPA-containing thermal paper. The patent on Pergafast 201 expires in 2019, which is why further reductions in price differences between BPA-containing and phenol-free thermal paper are expected in the future. Additionally, new alternatives with other developers or other print technologies are developed, including the thermal paper products Alpha® Free and Blu4est®.

After an introductory literature search and hazard assessment of the six most relevant alternatives, it was detected that sufficient data are missing to be able to compare the hazards of BPA with alternatives, as most of the alternatives are only tested on a limited scale. Thus, due to missing classification and considerably higher DNEL values (prepared by the REACH registrant) for alternatives, it is complicated to assess the degree to which they are less problematic than BPA, and to which degree they are significantly different from each other. TGSA stands out as the only alternative, which is skin sensitising, and may be considered critical as skin exposure is the dominant exposure pathway by using point-of-sales receipts and many other applications of thermal paper.

2.2 Chemical analysis of thermal paper

30 different products from both Danish suppliers and Danish users of thermal paper have been either purchased or collected. The received products were selected to ensure that different application fields and material types were represented, specifically with a focus on transportation, logistics and cultural events, and material types such as self-adhesive labels and cardboard/carton, primarily.

The six different developers BPA, BPS, BPS-MAE, TGSA, Pergafast 201 and D-8, which in the mapping were found to be the most widely used in thermal paper on the Danish market, have been determined in the received products. After content analysis of all thermal papers, one developer has been identified with the content of 0.4-1.6 weight%, which corresponds to the expected level of developers. As a result, there is no reason to think that other alternative/secondary developers are found in the selected products. Pergafast 201, found as a widely used alternative in thermal paper on the Danish market, was not among the identified developers in the selected thermal papers in this screening.

Migration tests of six products have been performed to acquire information on exposure scenarios when using thermal paper. The migration of developers was observed for three out of six thermal papers. For a single product consisting of paper, the amount of a migrated developer was up to 27% of the total content (see table below). In other cases, the migration was less than 1%. Migration from thermal paper made of paper was significantly larger than for thermal paper made of cardboard/carton or self-adhesive labels. The migration of four different developers was investigated. Since the diversity of material types for tested thermal papers may have a great impact on the migration of developers, the results from migration tests for different developers are not directly comparable.

TABLE: Summary of results for content analysis and migration tests for selected thermal papers.

		Total content	Migration after 5 sec.	Migration after 1 min.
Product No	Developer	[mg/kg]	[mg/kg]	[mg/kg]
11	TGSA	10000	19 (0,19%)	96 (0.98%)
12	BPS-MAE	8000	-	-
13	TGSA	9200	-	i.a.
16	D-8	3500	26 (0.75%)	130 (3.7%)
22	BPS	7600	1500 (20%)	2100 (27%)
23	D-8	16000	-	i.a.

- the result is under the detection limit (10 mg/kg).
i.a. not analysed.

2.3 Risk assessment

Exposure assessment
A realistic worst-case exposure scenario relevant for consumers regarding each of those three types of labels/tickets that displayed migration of alternative developers to artificial sweat were created.

For TGSA in a pick n' mix candy bag label, a scenario is assumed where a 6-year-old child sits with a candy bag in her hands having sweaty palms for 2 hours, e.g. while she watches a movie.

For D-8 in a cinema ticket, it is assumed that a 6-year-old child sits and fiddles with the ticket with sweaty hands and has skin contact for up to 2 hours.

For BPS in a parking ticket, it is assumed that an adult person has skin contact with the ticket in her pocket for approx. ½ hour.

Based on the measured surface area of the ticket and the degree of migration, the following dermal exposure scenarios were estimated:

TGSA, pick n' mix candy bag label:	11 µg/kg lgv /day
D-8, cinema ticket:	25 µg/kg lgv/day
BPS, parking ticket:	26 µg/kg lgv /day

Hazard assessment
For the relevant alternative developers TGSA, D-8 and BPS, the introductory hazard assessment was followed by a more detailed assessment of data on substances. BPS is the most examined developer, and a range of recent publications were found on this substance regarding the toxicological properties that indicate that this substance has corresponding adverse effects as BPA. For TGSA and D-8, the scope of accessible data is very limited, and the available data provide very scarce information.

In Appendix 1, the toxicological data have been described and assessed, and, based on these data, the tolerable exposure levels for skin contact (DNEL values for consumers) were calculated:

When calculating DNEL values, it should be converted from an oral exposure in animal testing to dermal exposure, which can be done in two different ways. The conventional method for calculation uses the relation between the oral intake % and the dermal absorption % to calculate

the dermal tolerable dosage. Since the absorption is usually lower at dermal exposure in relation to the oral exposure, the DNEL for dermal dosage is often higher than the oral DNEL.

Knowledge about the substance BPA indicates that this substance is more toxic upon skin contact than in the case of oral intake, because the substance by oral intake is quickly metabolised and deactivated in liver, as blood from intestines is led directly to the liver. However, this is not the case for skin absorption. As this may also be relevant for the alternative developers with a high structural resemblance with BPA, an alternative calculation is carried out for the dermal DNEL by taking this aspect into consideration.

TABLE: Dermal DNEL values for BPS, D-8 and TGSA calculated conventionally and taking the decreased metabolism into consideration.

	BPS	D-8	TGSA
DNEL dermal (conventional method)	0.15 mg/kg lgv/day (I) 0.022 mg/kg lgv/day (II)	0.30 mg/kg lgv/day	0.83 mg/kg lgv/day
DNEL dermal (decreased metabolism)	0.015 mg/kg bw/d (I) 0.0036 mg/kg bw/d (II)	0.03 mg/kg bw/d	0.08 mg/kg bw/d

Note that several DNEL values (I and II) have been calculated for BPS, which means that most recent tests indicate a lower DNEL than the DNEL value that can be calculated from the data accessible in the existing REACH registration.

Risk characterisation

In the risk assessment, the calculated exposure values for all three alternative developers with their respective tolerable exposure levels (i.e. DNEL values), and risk characterisation ratio (RCR = exposure/DNEL) is calculated:

	Calculated dermal exposure mg/kg/day	DNEL dermal (conventional) mg/kg lgv/day	RCR (conv.)	DNEL dermal (decreased metabolism) mg/kg lgv/day	RCR (metab.)
TGSA, pick n' mix candy bag label, child	0.011	0.83	0.01	0.08	0.14
D-8, cinema ticket, child	0.025	0.30	0.08	0.03	0.83
BPS, parking ticket, adult	0.026	0,15 (I) 0.022 (II)	0.17(I) 1.2(II)	0.015 (I) 0.0036 (II)	1.73(I) 7.2(II)

TGSA and D-8

When calculating RCR with conventionally calculated DNEL values and calculations, where DNEL (decreased metabolism) is applied, RCR values are found in the interval 0.03 to 0.83 for D-8 and TGSA, which is why no direct health-related risk is considered relevant to these scenarios. However, it should be noted that TGSA is skin sensitising, while D-8 is suspected to be skin sensitising. For this effect, it is not possible to calculate a DNEL value, because the threshold values for skin allergy are very complicated to determine and require a certain range of data. Thus, skin contact with these substances must be entirely avoided not to risk the development of a skin allergy. Here, especially long-term contact with sweaty hands is unsuitable.

BPS

Here, the risk assessment based on DNEL (decreased metabolism) is seen as more relevant than the application of DNEL by the conventional method, as the data indicate that BPS is metabolised and deactivated in the same way as BPA. For the calculated DNEL values where the metabolism conditions are considered, RCR values are found at 1.7 and 7.2, which indicates an unacceptably increased risk. Though, it should be mentioned that the uncertainties in exposure assessment (most likely over-estimated) and uncertainties in determining DNEL values lead to the fact that this type of conclusion is uncertain, and that better and more representative data for consumer exposure is needed to make a clear conclusion.

Hence, ECHA/RAC (2015) found BPA in point-of-sales receipts with an RCR value of 0.5 for consumers' exposure on the basis of a much larger amount of migration data. The EU restrictions on BPA in point-of-sales receipts are, thus, primarily based on the exposure of point-of-sales employees, where the calculated RCR values reached a value of 7.

Overall assessment

This report contains limited data for the substances TGSA, D-8 and BPS related to migration from thermal paper (a single set of test data for each substance). This, together with uncertainties in both exposure estimates and DNEL calculations, does not provide a foundation for representative risk assessment conclusions on the usage of thermal paper. Even for the concrete product assessments mentioned above, the uncertainties are too great regarding the exposure and DNEL estimates to allow for a clear conclusion.

The increased knowledge about the harmful effects of BPS strengthens the assumption of BPS having harmful effects similar to those of BPA. The use of alternatives with allergenic properties may be considered worrying in products with skin contact, since the migration risk must be considered problematic.

This report indicates that increased and more systematic knowledge of the harmful effects of the alternative substances and their migration from point-of-sales receipts is needed to obtain a basis for more accurate risk assessments.

3. Introduction

Today, thermal paper, i.e. heat-sensitive paper, is used for many different purposes, e.g. in point-of-sales receipts, parking tickets, labels, bank and ATM receipts, and tickets for public transportation and boarding cards. The thermal paper is easy to use for these purposes, as no ink is required to develop the desired print. The print development takes place only by exposing the paper to heat. The paper contains a so-called developer: a chemical substance that ensures that the colour appears in the paper. A frequently used developer is bisphenol A (BPA), where receipts are the isolated largest source to human exposure to BPA even though BPA in thermal paper only constitutes a fraction of the total usage of BPA (Chemsec, 2017). In the recent years, the usage of BPA as a developer has been in focus due to the CLP classification (repr. 1B) of BPA, and that is why the focus is also on thermal paper as a notable potential for reducing the exposure to BPA.

Hence, the usage of BPA in thermal paper will be restricted to 0.02 weight% from January 2020 in EU (Regulation (EC) No. 1907/2006), i.e. considerably lower than the amount used to achieve the effect as a developer in thermal paper. This, along with the classification of BPA as toxic for reproduction (Repr. 1B H360F), is assumed to give rise to an increase in usage of other developers in thermal paper as an alternative to BPA.

If one bisphenol is prohibited or regulated, other bisphenols are often used as an alternative, e.g. one of the examples is bisphenol S (BPS), which today is used as an alternative to BPA in thermal paper. The challenge of this approach to substitution of a problematic substance is, that when a substance has similar physicochemical properties, usually it also has similar toxic properties. For example, BPS is currently suspected to have carcinogenic, mutagenic or reprotoxic (CMR) properties (CoRAP). The development within developers in thermal paper is, thus, closely followed by authorities and the European Chemicals Agency (ECHA), interested parties in the value chain as well as research communities, who, among others, investigate the occurrence and content of new developers, and alternative technologies for thermal paper, e.g. digital solutions.

The usage of thermal paper on the market is not expected to decrease in the nearest future, but changes in the usage and new developers are expected to emerge because of legislation. To avoid regrettable substitution, where a problematic substance is substituted by a new substance that also turns out to be problematic, a great emphasis is laid on acquiring knowledge on those developers that substitute BPA in thermal paper.

Therefore, this report provides a mapping of the developers used in products on the Danish market. By collecting and updating the existing knowledge on the environmental and health effects, this report provides an assessment on the extent to which the Danish consumers and persons who handle thermal paper in their work are under a risk of being exposed to developers in thermal paper.

3.1 Aim

The main aim of this project is to provide an overview of the usage of developers in thermal paper in Denmark. The most recent knowledge on the toxic properties of developers is acquired by reviewing existing literature with an aim to assess whether the usage of alternatives to BPA constitutes a risk to persons, who are in contact with thermal paper.

4. Thermal paper–value chain and usage

Thermal paper has been used for commercial purposes since the 1960s, and today it is used in many places that require fast physical prints. This includes the following:

- point-of-sales receipts in retail industry
- tickets for parking/transport (train, bus, etc.), cultural events (cinemas, sport, theatre, etc.)
- packaging labels/thermal paper labels
- receipts from lotteries/gaming
- boarding cards for flights
- receipts from banks, gas stations and bottle recycling machines.

The largest part of thermal paper used in Denmark is produced by Mitsubishi HiTec Paper Europe GmbH, Koehler Paper Group, Kanzan (German manufacturers), and Jujo Thermal (Finnish manufacturer).

Thermal paper is imported to Denmark from foreign manufacturers via so-called converters, who cut the paper in suitable rolls. After that, the receipt rolls are sold directly to the user in retail, transportation sector etc. or via distributors to the user. In Denmark, mainly two converters dominate the market: the largest with a market share of approx. 75 % and the other with a market share of 20-25 %. Only one example of a user of thermal paper, who imports thermal paper from a converter in Sweden themselves, has been identified, i.e. only one user has informed that they import thermal paper from another supplier than the two converters on the Danish market.

The structure of thermal paper is illustrated in FIGURE 1 from Christensen et al. (2014). As it can be seen, the back and top coats are not always present in the structure of thermal paper, but can be used as a protective layer for applications, where longer duration of paper and print is required. The developers in thermal paper ensure that the text appears on the paper when heat is applied as descried in the same report.[1]

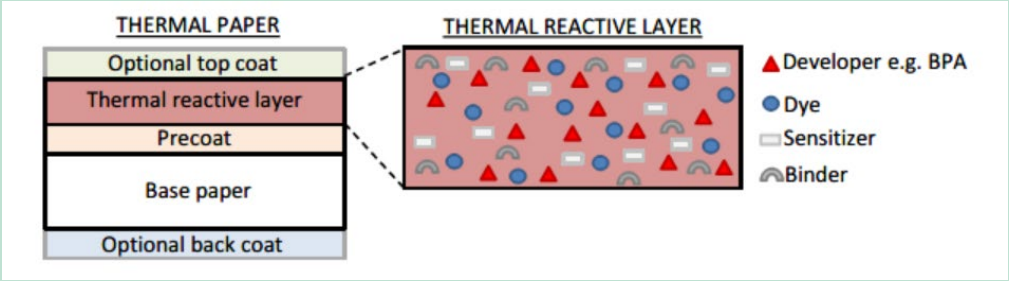


FIGURE 1. Structure of thermal paper. Source: Illustration from Christensen et al. (2014).

[1] A more detailed description of thermal paper may be found in Christensen et al. (2014).

5. Survey on developers in thermal paper

5.1 Method

5.1.1 Internet and literature search

The information acquired in interviews with companies in the value chain of thermal paper (section 5.2) has been compared and supplemented with the knowledge acquired from the internet and literature searches. The literature study is built on the report by Christensen et al. (2014) and is,thus, primarily focused on literature published after this report. A central scientific source is the review of BPA and alternative developers in thermal paper by Björnsdotter et al. (2017a), while important sources to commercially available alternatives as well as the consumer and market data on usage of thermal paper and developers are Chemsec (2017) and ECHA (2018). The internet search is specifically used to achieve detailed information on products, e.g. the alternative to traditional thermal paper called Blu4est®, as mentioned in interviews.

5.1.2 Interviews with interested parties regarding thermal paper

Companies in the entire value chain of thermal paper have been contacted and interviewed either via phone or e-mail, if the company requested written questions. This includes:

- three European manufacturers, who are all suppliers to the Danish market
- the two primary converters in Denmark (see chapter 4)
- two Danish distributors/dealers of thermal paper
- six different users of thermal paper from retail industry, gaming industry, postal services and cinemas.

Furthermore, the two interest organisations European Thermal Paper Association (ETPA) and Confederation of European Paper Industries (CEPI) have been contacted; however, they did not want to provide any information.

The interviews dealt with contents and consumption of developers, development of new developers and estimates of the market development, including new technologies as alternatives to thermal paper. First, the distributors of thermal paper were contacted and interviewed. The distributors have referred to converters, who in relation to interviews have referred further back the value chain to their manufacturers. Finally, users of thermal paper have been contacted.

The users selected for interviews represent a variety of different applications of thermal paper on the Danish market. All are large companies in the Danish market, e.g. retail store chains, cinema chains, and similar, and are present in all of Denmark. This way, these interviews can provide an insight into which types of thermal paper are available on the Danish market in great volumes. However, the interviews do not provide information regarding the choice and occurrence with smaller size users, e.g. independent stores, kiosks, cinemas, etc., who are not members of chains. Thus, this information is as much as possible covered via converters, who import and resell thermal paper. Generally, the users have been able to provide information on the underlying causes for the choice of thermal paper and on the consumption and new opportunities to reduce the usage of thermal paper. However, the users' knowledge on the contents of developers has been limited, and the users typically were not able to see the difference between BPA-free and phenol-free, which is why this information has been acquired further back in the value chain.

5.2 Developers on the Danish market today

Thermal paper can generally be divided into three categories according to the type of the used developer:

- BPA-containing
- BPA-free
- Phenol-free.

The information on the specific substances used as developers is in many cases confidential, among others, due to competition, and companies mention developers according to the above categorisation to varying degrees. However, the attempts have been made to clarify, which specific developers can be found within these three categories.

According to the largest converter, the above-mentioned categories in Denmark may be understood in such a way that BPA-free thermal paper contains BPS, while phenol-free thermal paper contains the developer Pergafast 201. Furthermore, the converter, who has approx. 75% market share, states that only three different developers are used on the Danish market: BPA, BPS and Pergafast 201.

One foreign manufacturer expresses a strong presumption that a competitor has thermal paper with D-8 in the top coat on the Danish market. The usage of BPA, BPS, Pergafast 201 and D-8 is also confirmed by another manufacturer, who adds that they use many other developers in their products, but they do not wish to disclose which ones. However, it is uncertain whether all or only a few of these products are found on the Danish market, since the manufacturer does not wish to disclose this. According to these interviews, there is some likelihood that thermal paper with D-8 is found on the Danish market. The Danish converters are not informed whether developers other than BPA, BPS and Pergafast 201 are found in thermal paper on the Danish market.

According to the Danish converters, there is a great difference between the users of thermal paper in relation to their knowledge and requirements to the specific developers. Some users are not aware or have no opinion on, which developers are used in their thermal paper. Among the interviewed users, a large supermarket chain and a chain of specialty stores have actively refused to use thermal paper containing BPA, and another chain of specialty stores has actively chosen to purchase phenol-free thermal paper. One converter also informs that a few large retail store chains have deliberately chosen to use phenol-free thermal paper, while another has chosen to use thermal paper containing BPA since legislation does not restrict it. All completed interviews indicate a tendency of more large chains (supermarkets and retail stores) take a stand on the issues regarding BPA in thermal paper and have typically chosen a BPS-containing or phenol-free thermal paper, while smaller users (e.g. small retail stores outside chains etc.) often purchase the cheapest thermal paper without paying attention to the contents of BPA.

In general, several alternatives to BPA in thermal paper have been identified already before. According to Christensen et al. (2014), the US EPA (2012) identified 19 alternatives either being in use (13 alternatives) or having been assessed to have a potential for usage in thermal paper based on their physicochemical properties. The overview by Christensen et al. (2014) achieved confirmation from the manufacturers of the usage of five of these alternative developers in thermal paper/thermal labels on the European market (see TABLE 1), except for UU that was assessed to be used only to a smaller degree. The same report concluded that the most widely used alternatives to BPA used in thermal paper in Europe were BPS and Pergafast 201. According to the completed interviews, this overview corresponds to the current situation on the Danish market.

TABLE 1. Most widely used alternatives to BPA-developers in thermal paper on the European market in 2014. Source: Christensen et al. (2014).

Application Category	Receipts from thermal paper	Labels
BPA-free	BPS (bisphenol)	D-8 (phenol) D-90 (bisphenol)
Phenol-free	Pergafast 201 UU	

In a mapping of bisphenols on the Swedish market by the Swedish Chemicals Agency (Kemikalieinspektionen (2017)), alongside the summary of studies and surveys with results also described in Christensen et al. (2014), a screening of patents was carried out, where 40 alternatives to BPA were identified, where some, i.e. several *tert*-butyl substituting bisphenols, had the potential of becoming alternatives for use in thermal paper. It is also mentioned that these alternatives have similar properties to BPA, and, thus, cannot be considered realistic BPA-alternatives.

In a recent study from 2017 (Björnsdotter et al., 2017b), 141 different samples of thermal paper from the Netherlands, Spain, Sweden and Norway were analysed with an aim to identify the used developers. A screening of 100 samples of thermal paper receipts as well as 41 other samples from cinema tickets, bus and train tickets, boarding cards, labels for weighing of fruit, etc. was carried out. The receipts showed either a content of one developer or a mixture of developers (typically a higher content of one primary developer and smaller content of a secondary developer); the receipts with traces (percentage or permille of the normal content level) of developers or without developers were considered as non-existent in thermal paper. BPA was found in 55% of the receipts, and BPS and Pergafast 201 were found in 21% of receipts each, which makes the BPA the most commonly used developer. In general, it was found that there was a great difference between the type of developers used in products in the four European countries. It was concluded that BPA, BPS, Pergafast 201 and D-8 are the most widely used primary developers (see FIGURE 2), which corresponds to the situation on the Danish market according to company statements. Furthermore, three new developers were identified alongside the primary developer: D-90, TGSA and BPS-MAE. These were found in small amounts (typically 3-10 times less than the primary developer). According to the authors, this indicates a possible cross-contamination during the production process and/or use of recycled paper.

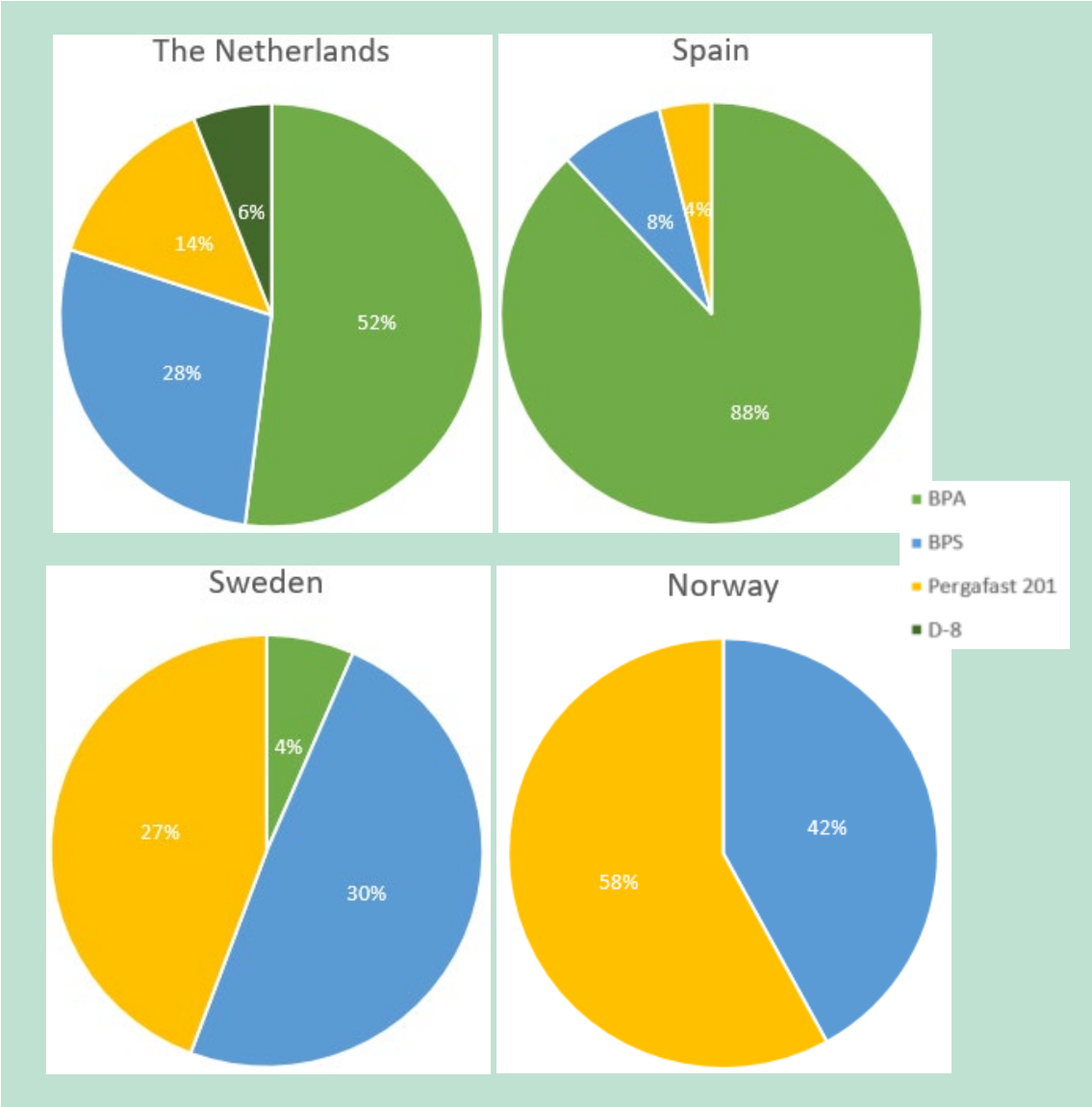


FIGURE 2. Primary developers identified in thermal paper in all four countries, where samples originate from. Source: Data from Björnsdotter et al. (2017b).

In a parallel study carried out in Switzerland in 2015 (Goldinger et al., 2015), 124 samples of thermal paper were examined to identify the most widely used developer(s). Samples included, among others, shop receipts, receipts from ATMs, parking tickets, bus tickets, etc. The study found samples with BPA, BPS, Pergafast 201 and D-8 (see TABLE 2). In samples with D-8, traces of BPS were also identified, but none of the samples contained more than one developer in significant amounts.

Besides their own study on developers in thermal paper in four different countries as described above, Björnsdotter et al. (2017a) have also prepared an extensive review of literature from 2010-2017 on, among others, the usage of BPA and alternatives in thermal paper. This review covers studies that are not limited to either Denmark or Europe. The above-mentioned results from Björnsdotter et al. (2017b) indicate great differences between the occurrence of BPA in thermal paper depending on which European country the sample originates from; also, between countries with which Denmark often compares itself regarding the content of chemical substances in products. This variation and the results achieved on a limited number of samples from each country indicates that one should be very cautious with transfer of data in one or several of the countries onto the Danish circumstances. In general, thermal paper with BPA has been

found at a frequency of everything from 11 % to 100 % in different studies. This review mainly states that BPA and BPS are found at a high frequency in several studies on point-of-sales receipts and many other products of thermal paper, such as cinema tickets, parking tickets, bus and train tickets, boarding cards and luggage labels. Other alternatives such as Pergafast 201 and D-8 have only been identified in more recent studies.

The above overview of many different studies shows overall that BPA, BPS and Pergafast 201 was used in 2014 and are still the primarily used developers in 2018 in thermal paper on the European market. The same scenario is found in literature, i.e. the three mentioned developers being the mainly used developers used internationally in thermal paper; however, there are great differences in the occurrence of the developers between countries. As mentioned in chapter 5, the companies in the value chain on the Danish market inform that these three developers, i.e. BPA, BPS and Pergafast 201, are also the three developers used on the Danish market, while some manufacturers express that specifically D-8, which is observed in many international studies, can be found on the Danish market. The studies and interviews show an extensive development in this field over a few years as to the share of the thermal paper with each developer and the differences between countries. This, together with variations in the number of samples (from 1 to 100+) and the specific application of samples (from point-of-sales receipts and parking tickets to toilet paper) in each of the studies indicates that one should be very cautious on making direct comparisons and interpreting concrete tendencies from the literature, but it provides a valuable insight into what can be specifically found on the markets.

5.2.1 Content of developers

It has not been possible to collect additional information on the scope of developers in thermal paper in connection with the interviews in this mapping. In 2014, the manufacturers stated (Christensen et al., 2014) that thermal paper with BPA contains approx. 1 weight% (i.e. 10,000 mg/kg) of developer, while thermal paper with BPS would typically require a 20% higher content of developer (i.e. approx. 12,000 mg/kg) compared to a BPA-containing paper. International studies in the period from 2010-2012 are mentioned in the same report and show a BPA content of approx. 8,700-28,000 mg/kg for BPA-containing thermal paper, while contents of BPS in BPA-free thermal paper are referred to as being up to 22,000 mg/kg (Christensen et al., 2014).

In a review from 2017, a range of reports and publications on the contents of developers in thermal paper have been reviewed, and an overview has been provided on results of these studies on both the occurrence and contents of BPA, BPS, Pergafast 201 and D-8 in point-of-sales receipts, as well as the occurrence and contents of BPA and BPS in other paper products[2] (Björnsdotter et al., 2017a). Here, based on several studies, it is indicated that BPA-containing point-of-sales receipts have been found to have a content of BPA from approx. 3 mg/kg to 42,600 mg/kg in Europe. Goldinger et al. (2015) detected Pergafast 201 and D-8 in concentrations up to 8,200 mg/kg and 13,200 mg/kg respectively, while the average content of BPA in BPA-containing point-of-sales receipts were found to be 13,500 mg/kg. Similarly, Östberg and Noaksson (2010) found high concentrations of BPA (5,000-32,000 mg/kg) in, among others, parking tickets, line numbers, ATM receipts, gaming receipts, flight, bus and train tickets as well as labels for weighing fruit/vegetables in supermarkets (Björnsdotter et al., 2017a).
Björnsdotter et al. (2017a) mainly conclude that there is a range of examples of thermal paper products with high concentrations of BPA (5,000-32,000 mg/kg), and that the concentration of BPS, Pergafast 201 and D-8 in point-of-sales receipts are on the same level as BPA. Examples of developer occurrence and concentration in thermal paper samples taken in Europe are shown in TABLE 2.

[2] Some parts of these paper products are thermal paper, e.g. parking tickets, ATM receipts, cinema tickets, etc., but are not limited to thermal paper. The occurrence and average level/interval of the content of developer are specified in relation to each application, i.e. at product level.

TABLE 2. Examples of contents of developers in thermal paper in Europe.

Developer	Number of samples (number of samples with quantifiable content)	Concentration, average (interval) [mg/kg]	Reference	Sample material
BPA	12 (7)	11,400 (8,700-17,000)	Lassen et al. (2011)	Different samples of thermal paper
	1	10,800	Christensen et al. (2014)	Thermal paper with BPA
	124 (100)	13,500 (5,600-30,400)	Goldinger et al. (2015)	Different samples of thermal paper
BPS	1	11,600	Christensen et al. (2014)	Thermal paper with BPS
	37 (4)	11,200 (8,300-12,600)	Goldinger et al. (2015)	Different samples of thermal paper
Pergafast 201	1	10,400	Christensen et al. (2014)	Thermal paper with Pergafast 201
	37 (11)	5,400 (3,300-8,200)	Goldinger et al. (2015)	Different samples of thermal paper
D-8	37 (9)	5,400 (3,400-13,200)	Goldinger et al. (2015)	Different samples of thermal paper

5.2.2 Price

The price of thermal paper without BPA has developed extensively during the recent years. In 2011, parts of the Danish retail industry indicated that thermal paper with BPS was approx. 100% more expensive than thermal paper with BPA, while phenol-free thermal paper was indicated to be approx. 400 % as expensive as thermal paper with BPA (Lassen et al., 2011). Furthermore, in 2014 the BPA-containing thermal paper was indicated as the cheapest product, but a tendency of falling prices of BPA-free alternatives was detected due to increasing demand. The prices of thermal paper with alternative developers were estimated by three manufacturers in relation to the price of BPA-containing thermal paper; BPA-free (BPS) thermal paper cost 5-12 % more, bisphenol-free (D-8 and D90) thermal paper cost 10-20 % more and phenol-free (Pergafast 201) thermal paper 10-25 % more than BPA-containing paper. A distributor estimated prices for BPA- and bisphenol-free paper being slightly higher than the manufacturers' estimates (Christensen et al., 2014).

In interviews for this survey, this development is generally confirmed by manufacturers, converters and users of thermal paper. A converter informed that the prices of thermal paper with both BPA and BPS are basically identical, which is highlighted by the fact that they often do not distinguish between these two products, and unless the customer specifically asks for thermal paper with BPA, the customer will often receive thermal paper with BPS. The same converter informs that the price of thermal paper with phenol-free alternatives is 16-18 % higher than for thermal paper with BPA/BPS, where the corresponding price difference three years ago was 30-35 %. The other converter estimates, however, that BPA-free thermal paper is more expensive than BPA-containing paper and considered the thermal paper with phenol-free alternatives being "considerably more expensive" and more expensive than BPA-free thermal paper.

In this survey, a manufacturer confirms a tendency for a higher price, when changing from BPA to BPA-free and again to phenol-free thermal paper as stated in Christensen et al. (2014). The price of thermal paper increases when the developer is changed from BPA to BPA-free, to D-8 and to Pergafast 201.

In general, there has been a considerable reduction in price differences compared to previous prices, which is also confirmed by a large supermarket chain. However, Pergafast 201 is still the most expensive developer. Pergafast 201 is produced by BASF, who holds a patent on this product, but since the patent expires by December 2019, this will allow an opportunity for competition on this specific alternative developer, which could possibly reduce the price.

A manufacturer mentioned that the cost price of thermal paper is only to a very small degree is determined by the cost price of the developer, which is why it does not explain the large differences in sales price of thermal paper with different developers. Yet, it can explain why some companies say that the price differences of thermal paper with different developers are gradually declining, and the initial price differences may be a result of development costs etc. in relation to the identification and implementation of new developers in addition to the basic extra price, because it simply is an alternative. Some companies mention that the users' expenses for thermal paper are low in relation to other operational costs in the companies, which is why an increased cost of thermal paper with alternative developers can be considered being insignificant from a user's perspective.

5.2.3 Properties

To be applicable on the market, it is important that the thermal paper has the necessary properties. For developers in thermal paper, it is primarily the stability that is in focus regarding the assessment of properties. A manufacturer informs that phenol-free products have better properties than BPA-containing products, and they have, thus, been used in thermal paper for 10-15 years with higher requirements to stability, e.g. lottery coupons and tickets. On the contrary, requirements for stability and durability are often lower in, e.g. point-of-sales receipts in parts of the retail industry, where e.g. grocery stores and kiosks do not need a great durability, which is why phenol-containing developers are technically sufficient. In retail industry, there could be other reasons, such as CSR profile and environmental and health considerations (e.g. reduced employee exposure to BPA), which have led to the rejection of BPA-/phenol-containing developers as described before even though the technical properties of thermal paper with BPA are sufficient.

This information corresponds to the information reported earlier, where Christensen et al. (2014) describes BPA as the least stable developer compared to the other five relevant alternatives (BPS, Pergafast 201, D-8, D-90 and UU). The phenol-free alternatives are indicated as being the most stable developers, which corresponds to information received from the manufacturer described above and are, thus, applicable in thermal paper that must be saved for a longer period of time after printing.

5.3 Consumption of developers

To follow the development of substitution of BPA with BPS and other developers in thermal paper, ECHA has made a survey on the usage of BPA with manufacturers selling thermal paper in the EU (ECHA, 2018). ECHA's survey shows (see FIGURE 3) a twofold increase in the consumption of BPS in thermal paper from 2016 to 2017, whereas the consumption was relatively stable before (2014-2016). The consumption of BPA during this period has remained unchanged, but since the total consumption of developers has been increasing (estimated 7% increase from 2016 to 2017) in the EU, BPA constitutes a smaller market share of developers in thermal paper. From 2014 to 2015, an increase in the usage of other developers can be observed, but after that the level has remained unchanged. Approximately 30% of the thermal paper in the EU is imported from China, India, Japan, Korea and USA; regions that are not included in ECHA's survey. ECHA's survey concludes that there are early signs that the European manufacturers have started to substitute BPA with BPS in thermal paper. ETPA is cited in ECHA (2018) to expect a continuous increase in the share of thermal paper with BPS during the upcoming years, even though the scope of the increase is dependent on the price development of phenol-free alternatives.

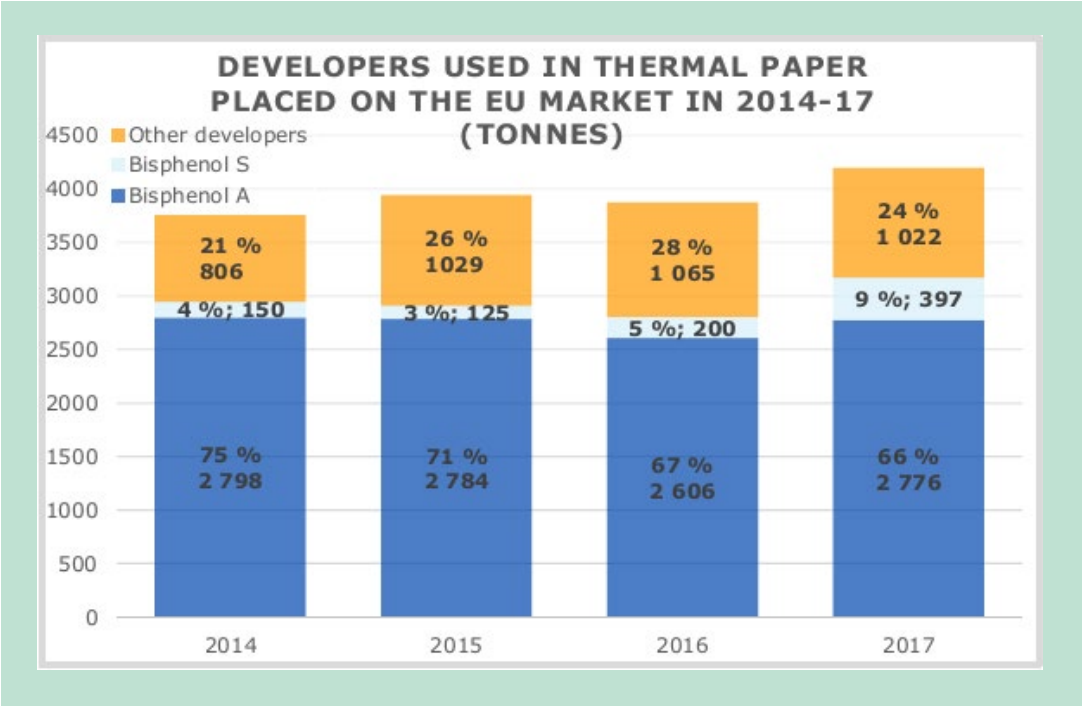


FIGURE 3. Developers used in thermal paper produced and sold on the European market from 2014-2017 (for ETPA members). Source: Graph from ECHA (2018); based on data from ETPA.

In general, the sales of thermal paper are increasing in the EU (ECHA, 2018), just like in 2014 (Christensen et al., 2014). The two converters confirm that thermal paper with BPA is still the primary product, but the sales of BPA-free thermal paper are increasing in Denmark. The largest converter informed that three years ago they did not sell phenol-free thermal paper, but now this type of thermal paper constitutes approx. half of the sales of the thermal paper. The same converter predicts the development in using BPA and alternative developers in thermal paper in Denmark as illustrated in TABLE 3 and expects that the usage of phenol-free thermal paper will increase considerably in the next years. Additionally, it is expected that many will change to phenol-free thermal paper instead of using BPS-containing thermal paper when the restrictions on BPA-containing thermal paper will come into force in 2020.

TABLE 3. Estimated development of market share of thermal paper on the Danish market. Source: Converter.

Thermal paper	2015	2016	2017
BPA-containing	60 %	50 %	30 %
BPS- containing	25 %	35 %	35 %
Phenol-free (Pergafast 201)	15 %	25 %	35 %

The largest converter informs that they do not always make a distinction between thermal paper with BPA and BPS, as there is no price difference (as described in section 6.2.2 above), which means that they are free to choose to deliver BPS-containing thermal paper instead of BPA-containing paper, if in stock. Another distributor confirms this, which may contribute to an increased market share of BPS-containing thermal paper instead of BPA-containing thermal paper on the Danish market. Furthermore, the largest converter is planning to phase out the BPA-containing thermal paper from their product range; however, due to closing of several manufacturers of raw materials for thermal paper on the Chinese market, which creates a shortage of thermal paper, the phasing out has not been completed. Stabilisation is expected during the last quarter of 2018, after which the phasing out can be completed. All other equal, this should lead

to a significant reduction of the market share of BPA-containing thermal paper on the Danish market.

The market share of thermal paper with BPA has, thus, declined both in Denmark and the EU. However, the market share of BPA-containing thermal paper is estimated to be reduced more in Denmark compared to the EU in general, and the usage of alternative developers in thermal paper has increased in Denmark compared to the status quo on the European market.

5.4 Users' opinion on developers in thermal paper

In the interviews, converters and distributors of thermal paper to the Danish market confirm that the price of thermal paper is typically the primary parameter that determines the choice of the purchased thermal paper when dealing with small companies, among others, small retail stores such as kiosks and greengrocers, stores that are not a part of a chain etc. The largest part of the interviewed users indicate that this trend is real, which means that the larger a company, the greater the probability that they have actively taken a stance regarding the content of developers in their thermal paper (see also section 6.2). Furthermore, it can also be related to the fact that large companies and retail chains have staff resources with specific responsibilities for environment and CSR, which is why they often choose phenol-free alternatives to BPA-containing thermal paper to reduce the employees' exposure to BPA, bisphenol- and phenol-based developers going beyond legislation as it is now and in 2020. Similarly, these statements indicate that small retail stores with lower requirements to quality, stability and durability of the print on thermal paper often use BPA-containing (alternatively BPS-containing) thermal paper.

As mentioned in section 6.2.2, each company, among others, distributors, conclude that the users' expenses for thermal paper are low compared to other operational costs, which is why an increase in cost of 15-20 % for using phenol-free thermal paper may be considered insignificant.

The arguments for deselecting BPA-containing thermal paper and the use of phenol-free thermal paper are primarily rooted in the wish to protect own employees against the exposure to BPA and bisphenols, according to two users within retail, while less focus is paid to the customers' exposure.

5.5 New commercial developers

The foreign manufacturers (all) work on the development of alternative developers according to the interviewed manufacturers. Not everybody wishes to talk about this development due to trade secrets, launching of new products or competition within the industry. Thus, the alternatives identified in this survey consist of new developers that are commercially available from manufacturers.

Koehler Paper Group, as mentioned in chapter 5, offers Blu4est® as an alternative thermal paper product, which is marketed as environmentally friendly with no contents of chemical developers. The print on thermal paper appears because of a physical mechanism rather than a chemical reaction, because Blu4est® paper contains small bubbles with colorant, which burst when affected by heat from the print head and, thereby, release colour and develop the print. The thermal paper can be used in the existing thermal printers, and the print is stable according to their product description. The new thermal paper from Koehler Paper Group is not available on the Danish market yet, but is used in approx. 200 companies in the German-speaking countries. Blu4est® is approx. 50% more expensive than BPA-containing paper (Chemsec 2017; Koehler Paper Group's website; presentation from Koehler 2017). However, Koehler expects that this price difference will be significantly reduced when the product is produced in large quantities.

The American manufacturer Appvion offers the product Alpha® Free as an alternative without phenol-based developers, because the developer is based on vitamin C instead. The product is

used in a small segment within organic food products in USA, and the price of the product is 100% more expensive than BPA-containing thermal paper (Chemsec, 2017).

5.6 Market evaluation, alternative technologies and exposure

According to one converter, the sales volume of thermal paper in Denmark has been stable during the recent years, while it has increased slightly in Europe and globally.

Despite this, a converter has informed that the consumption of thermal paper in supermarkets has declined by 50% in connection with the opportunity to ask the customer whether they wanted the receipt rather than just printing the point-of-sales receipt automatically. A large supermarket chain has started a number of initiatives to reduce the usage of point-of-sales receipts; e.g. the point-of-sales receipt for small purchases is only printed if the customer wishes it, bottle deposit will be paid to payment cards in future, and it is possible to issue electronic receipts instead of physical ones. The electronic receipts are used as an alternative offer instead of physical point-of-sales receipts in many retail chains (e.g. more than 5,000 stores, including many retail chains, have subscribed to Storebox[3]), and the supermarket chain expects that electronic receipts can replace the physical point-of-sales receipts probably during the next 3-5 years.

However, another large supermarket chain states that point-of-sales receipts still are and will be important, as they are also used as information to the customer about opening hours, marketing on the backside etc. The supermarket chain informs that the number of point-of-sales receipts may be declining, but the length and point-of-sales receipts is increasing due to larger amounts of information.

On a global scale, it is expected that the consumption of thermal paper will increase (Chemsec, 2017). Nevertheless, the interviews showed estimates for either unchanged (manufacturers, converters and two users from retail sector) or declining (three users; retail, gaming and cinema) total consumption of thermal paper on the Danish market.

A manufacturer described that the European consumption is changing, so that some applications require smaller amounts of thermal paper due to digital alternatives such as electronic receipts, boarding cards via self-print or phones, payments for parking via phone and games in casinos with plastic cards, while the usage of thermal paper is increasing in other applications, e.g. considerable increase within logistics (receipts and labels) due to growing e-trade, growth within gaming market as well as growth within other labelling. Chemsec (2017) also describes a similar expectation regarding the decrease in application of thermal paper to point-of-sales receipts due to digital alternatives and the continuous total growth due to the large growth within logistics and e-trade.

A distributor estimates that in 10-20 years they might not live on selling receipts due to the expected fall in the usage of thermal paper; mainly due to the large chains, since e.g. the small kiosks are not able to deliver electronic receipts.

Thus, the mapping shows that opinions vary regarding the expectations about the total growth in sales and consumption of thermal paper. Many still believe that the usage of thermal paper for physical point-of-sales receipts with traditional purchases in retail stores, tickets, etc. will be reduced in the future and that more thermal paper will be used in connection with logistics due to the growing e-trade.

The companies have shown a great focus on digital alternatives to thermal paper with developers, i.e. the usage of electronic receipts and mobile solutions for payments, tickets, etc. This

[3] A service company offering digital receipts to companies and customers; https://dk.storebox.com/#/

corresponds to a higher degree to the alternative solutions identified and assessed as having the greatest potential by Christensen et al. (2014), where the most promising technologies for the reduction of the number of receipts and tickets were mentioned being mobile payments via apps (in-app-purchases and handling of receipts) and electronic receipts.

On the other hand, less focus has been on solutions for handling thermal paper to reduce the exposure to BPA, e.g. point-of-sales employees' contact with receipts. The interviews with users within the retail sector indicated that these more practically oriented solutions were implemented where it was necessary, which is why there is no specific focus when discussing alternative technologies to thermal paper. The implemented non-digital solutions include highly reduced handling of point-of-sales receipts by, among others, asking whether the customer wishes to receive a receipt, whether the customer takes the receipt from thermal printer him/herself, self-service point-of-sales line etc.; the solution has been described in the overview of alternative technologies by Christensen et al. (2014).

5.7 Hazard assessment of alternatives

This chapter provides a hazard assessment of BPA-alternatives known to be used in thermal paper in Denmark, i.e. BPS, Pergafast 201 and possibly D-8 as well as alternatives that are found in Norway and Sweden, i.e. D-90, TGSA and BPS-MAE. The aim of this assessment is to establish an overview of the possible effect of these substances, so that the substance hazard profiles can be compared with the hazards of BPA.

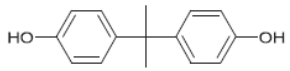
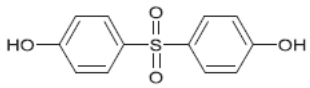
The assessment is based on data found on the website[4] of the European Chemicals Agency, where information was acquired on substance hazard classification and any special regulations under REACH. Thereafter, toxicological data in the substance REACH registry are searched for in relation to substance effects and dosis-response for these by indicating NOAEL (no observed adverse effect level) and LOAEL (lowest observed adverse effect level). It should be noted that data collected in this initial screening are not subject to specialist assessment but are only passed on from information in the REACH registrations.

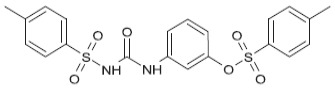
More relevant sources to these substances is the European Chemicals Agency background document for proposing restrictions for BPA in thermal paper. This report (ECHA, 2015) includes data and a preliminary assessment of all the above-mentioned alternatives except BPS-MAE, which is not included in this report. Similarly, the US EPA (2015) has created a summary on the toxicological data for alternatives to BPA in thermal paper, including the six above-mentioned, where, in addition to the assessment of concrete data, structure assessments (SAR) and assessment of possible *read-across* between data for substances have been carried out. Finally, a search for additional relevant data in TOXnet database has been performed, that, among others, includes assessments from US EPA´s Integrated Risk Information System (IRIS assessments) as well as search for other expert assessments/substance assessments that have been performed after ECHA (2015) and US EPA (2015) have assessed the alternatives.

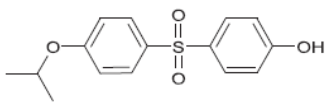
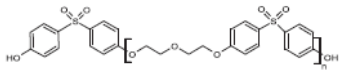
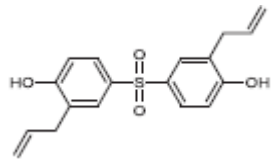
TABLE 4 shows the most relevant data for substances for the assessment of substance toxicological profile. Data, indicated in REACH registrations, are mainly the same data that have been analysed in ECHA (2015) and in US EPA (2015). Hence, the data from REACH registrations have been used as these registrations include more detailed information on the classification and DNEL values (*Derived No Effect Level* corresponding to a tolerable exposure level), which is not the case regarding the registrations from ECHA (2015) and US EPA (2015).

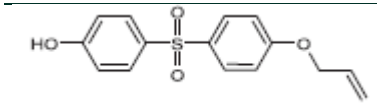
[4] https://echa.europa.eu/

TABLE 4. Hazard assessment (classification, most critical NOAEL/LOAEL values and DNEL values) for alternatives to BPA.

Name/CAS No./ Chemical structure	Name / CAS No. / Chemical structure				Other data
	Registration-tonnage (+ specific regulation)	**Classification**	**Most critical effects and NO-AEL/LOAEL**	**DNEL value consumers**	
BPA 80-05-7 	Registered 1,000,000-10,000,000 tons (and as SVHC on the candidate list. Use limitation as for thermal paper)	Eye Dam. 1 H318* Skin Sens. 1 H317* STOT SE 3 H335* Repr. 1B H360F* Aquatic Chronic 2 H411	BMDL (10) (o) = 9.0 mg/kg bw/d reduced weight of the kidneys in 2nd generation test	1 mg/m^3 (i) 0.002 mg/kg/d (d) 0.004 mg/kg/ (o) Values calculated from EFSA (2015) estimate	ECHA (2015): DNEL (o) = 0.004 mg/kg/d as external dosis DNEL (d) = 0.0001 mg/kg/d as internal dose Based on effects in mammary gland, the nervous system and the immune system US EPA (2015): RDT: M Nervous system toxicity: M Fetal development: H Fertility: M Cancer: M SS: M
BPS 80-09-1 	Registered 10,000-100,000 tons (none)	Repr. 2 H361f	RDT: LOAEL: 300 mg/kg/d (o): effect on body weight and damage in mammary gland of male rats. NOAEL: 100 mg/kg bw/d (o) Repr: LOAEL: 300 mg/kg/d (o): effect on fertility NOAEL: 60 mg/kg bw/d (o)	1.7 mg/m^3 (i) 1 mg/kg/d (d) 0.5 mg/kg/d (o)	ECHA (2015) and US EPA (2015): Description and assessment of available toxicological data. No calculation of DNEL. US EPA (2015): RDT: H Nervous system toxicity: M Fetal development: H Fertility: M Cancer: M Mutagen: M
Pergafast 201	Registered	Aquatic Chronic 2 H411*	RDT:	No data (i) 0.625 mg/kg bw/d (d)	ECHA (2015) and US EPA (2015): Description and assessment of

Name/CAS No./ Chemical structure	Name / CAS No. / Chemical structure				Other data
	Registration-tonnage (+ specific regulation)	Classification	Most critical effects and NO-AEL/LOAEL	DNEL value consumers	
232938-43-1 	Tonnage level specified as confidential information (none)		LOAEL: 150 mg/kg bw/d (o): increased liver and kidney weight. Change in liver cells and effect on blood picture NOAEL: 50 mg/kg bw/d (o)	0.625 mg/kg bw/d (o)	available toxicological data. No calculation of DNEL. US EPA (2015): RDT: M Fetal development: M Fertility: M Cancer: M

D-8 95235-30-6 	Registered Tonnage level specified as confidential information (none)	Aquatic Chronic 2 H411*	RDT: NOAEL: 50 mg/kg bw/d (o) No description of data.	0.38 mg/m^3 (i) 0.25 mg/kg/d (d) 0.25 mg/kg/d (o)	ECHA (2015) and US EPA (2015): Description and assessment of available toxicological data. No calculation of DNEL. US EPA (2015): RDT: M Nervous system toxicity: M Fetal development: M Fertility: M Cancer: M
D-90 191680-83-8 	Registered under EC No. 427-620-8, but without CAS No. Tonnage level specified as confidential information (none)	No classification	RDT: NOEL= 1000 mg/kg bw/d (o) Repr: NOEL= 1000 mg/kg bw/d (o) No description of data.	6.25 mg/m^3 (i) 4.17 mg/kg/d (d) 4.17 mg/kg/d (o)	ECHA (2015) and US EPA (2015): Description and assessment of available toxicological data. No calculation of DNEL. US EPA (2015): Nervous system toxicity: M Cancer: M
TGSA 41481-66-7 	Registered Tonnage level specified as confidential information (none)	Skin sens1 H317* Aquatic Chronic 2 H411*	RDT: NOAEL= 150 mg/kg bw/d (o) No description of data.	None DNEL values specified	ECHA (2015) and US EPA (2015): Description and assessment of available toxicological data. No calculation of DNEL. US EPA (2015): RDT: H Nervous system toxicity: M Fetal development: M Fertility: M Cancer: M SS: M
BPS-MAE 97042-18-7	Registered> 100 tons (none)		RDT: NOAEL= 1000 mg/kg bw/d (o) Repr: LOAEL: 500 mg/kg/d caused post-term pregnancy and prolonged labour NOEL = 100 mg/kg/d	17.6 mg/m^3 (i) 5 mg/kg/d (d) 5 mg/kg/d (o)	US EPA (2015): Description and assessment of available toxicological data. No calculation of DNEL. US EPA (2015): Nervous system toxicity: M Fetal development: M

	Fertility: M Cancer: M Mutagen: M

* Is also EU harmonised classification

(i): inhalation, (d): dermal, (o): oral, RDT: repeated dose toxicity, SS: skin sensitisation, M: moderate hazard category, H: high hazard category

By assessment of data in this table, the discussion on classification of environmental effects or DNEL values for inhalation have not been taken into consideration as these parameters are not important for this project in relation to the consumers' risk for exposure to these substances through point-of-sales receipts.

It should be noted that BPA has been assessed and, above all, tested much more thoroughly than the alternatives, which is why there is a much larger amount of information available for this substance. In case of alternatives, the tests are more limited, and the overall assessment of these substances is thus more insufficient. Lacking classification and relatively much higher DNEL values are the reason why the data for some aspects are entirely missing or are highly scarce. Especially, information on D-8, D-90 and TGSA is missing, as reporting of data in the registration of these substances is highly insufficient. Furthermore, it is not possible to assess, which data requirements must be met regarding the REACH registration for these substances, as the tonnage level for these substances (also for the substance Pergafast 201) has been indicated as confidential.

In their screening of substances, US EPA (2015) have presented the assessed hazard potential partly based on the concrete data and partly based on the structure-activity relationship models and read-across of data. For different hazard classes, they were scored from very low to very high (vL, L, M, H, vH). In those cases, where the score was moderate (M) or higher, this is stated in the table for the effects: repetitive dosage (RD), Neurotoxicity, Foster Development, Fertility, Cancer, Mutagenic effects and Skin sensitisation (SS).

The table shows:

- That data for the substance BPS indicates a certain concern regarding effects on fertility as the substance is classified as Repr. 2 regarding fertility.
- That the substance TGSA is considered skin sensitising.
- That the oral and dermal DNEL values for substances BPS, Pergafast 201 and D-8 all are < 1 mg/kg lgv/d (in the interval 0.25-1.1 mg/kg lgv/d), i.e. more than a factor 100 higher than DNEL values for BPA.
- That the oral and dermal DNEL values for substances D-90 and BPS-MAE are in the interval (4-5 mg/kg lgv/d) corresponding to a factor 1000 higher than DNEL values for BPA.
- That US EPA (2015) in their hazard screening indicates a moderate or higher score for between two (for D-90) and up to six problematic hazardous properties (for BPS).

By closer analysis of assessments and discussions in ECHA (2015) and US EPA (2015) and a complete assessment of data, it is possible that, in case of some alternatives, this would indicate an additional classification and potentially adjusted NOAEL/LOAEL values and DNEL values. This type of a follow-up analysis and a more in-depth assessment/description of substances will only be carried out for the relevant alternatives that are shown in the subsequent analysis program.

Finally, it must be mentioned that no additional expert assessments and substance assessments for the selected alternatives have been found in the data search.

5.8 Summary and conclusion

In general, the above mapping of developers in thermal paper shows that BPA, BPS and Pergafast 201 are the developers mainly used in thermal paper on the Danish market, while D-8 may also be used. This corresponds well with information that BPA, BPS and Pergafast 201 both in 2014 and today are the developers mainly used on the European market, and, likewise, the literature finds usage of the same developers internationally, including finding D-8 in several studies. Significant differences in frequency of each developer between countries are observed. The literature provides a good insight into which developers can specifically be found on the

markets, and which concentrations they are used in; however, one must take caution when directly comparing and interpreting concrete tendencies from the literature.

The sales of thermal paper are slightly increasing in the EU and are, according to the major part of the market, expected not to fall in the future, neither in the EU or in Denmark. It is expected that the application of thermal paper will change, as, among others, digital solutions reduce the share of the thermal paper used in e.g. point-of-sales receipts and tickets, while the usage of thermal paper in connection with logistics will increase due to growth in e-trade.

The share of thermal paper with BPA has decreased both in Denmark and EU. However, the share of BPA-containing thermal paper is estimated to be reduced more in Denmark than in the EU in general, and the usage of alternative developers in thermal paper has increased in Denmark in contrast to the status quo on the European market. Among the users of thermal paper, many chains have taken an active stance to the choice of developers in thermal paper, and many choose phenol-free alternatives to protect their employees against exposure to specifically BPA, but also bisphenol- and phenol-based developers in general. Also, in many places a number of practical measures have been taken to reduce the employees' physical handling of thermal paper, specifically point-of-sales receipts. On the opposite, there is a tendency that smaller companies have not actively chosen to deal with thermal paper with BPA, and they often purchase the cheapest, i.e. typically a BPA-containing thermal paper.

The contents of BPA as a primary developer in thermal paper is typically within the scope of 1 weight%. In the most recent literature for the European market, the examples show BPA contents of approx. 0.5-3 weight%. The content of BPS as a primary developer has typically been indicated being 120% of the corresponding BPA content in thermal paper. The literature provides examples that confirm this tendency: 0.8-2.2 weight%. In case of the alternatives Pergafast 201 and D-8, examples have demonstrated contents of the developer of approx. 0.5 weight% (0.3-1.3 weight%) in thermal paper. The international literature shows a range of examples on products of thermal paper with high BPA concentrations (up to 3.2 weight%), but generally, the BPA levels in Europe are as described above, just as the concentration of BPS, Pergafast 201 and D-8 in point-of-sales receipts are on the same level as BPA.

The price difference between thermal paper with BPA, BPS and phenol-free developers have been significantly reduced during the past few years. In 2011, the BPS-containing and phenol-free thermal paper were approx. two and five times more expensive than BPA-containing thermal paper, while the price of BPS-containing thermal paper today corresponds to or is slightly higher than BPA-containing thermal paper, and phenol-free thermal paper costs 16-18 % more than BPA-containing thermal paper. After the patent for Pergafast 201 has expired in 2019, further reduction in price differences between BPA-containing and phenol-free thermal paper are considered possible.

Technically, no disadvantages are connected to the usage of BPS or other identified alternative developers in thermal paper, as their properties, stability and durability of the print are typically better than in thermal paper with BPA. Entirely new alternatives identified by Appvion and Koehler Paper Group (thermal paper products Alpha® Free and Blu4est® respectively) are marketed as being both high quality and having long print durability. The environmental profile is also improved, because the companies use vitamin C as developer (Alpha® Free) and have based products on a mechanism without a developer (Blu4est®), respectively.

The preliminary literature search and hazard assessment of the six most relevant alternatives allowed to determine that sufficient data are missing to a high degree to be able to compare the hazards of BPA to alternatives, as most of the alternatives are only tested to a limited degree. Thus, based on the missing classification and considerably higher DNEL values for alternatives it is complicated to assess the extent to which they are less problematic than BPA and to which

extent they are significantly different from each other. However, TGSA stands out as the only alternative being skin sensitising, which may be critical, because skin exposure is the dominant exposure pathway when using point-of-sales receipts and many other applications of thermal paper.

Selection of alternative developers for an actual risk assessment was, thus, to a high degree based on the measurement results that appear in the content and migration tests, since a large spread in migration potential can exclude other alternatives with lower migration relevant to a subsequent risk assessment.

6. Chemical analyses of thermal paper

The content of six different developers has been determined in different types of thermal paper. These developers include BPA, BPS, BPS-MAE, TGSA, Pergafast 201 and D-8 (see **TABLE 4**), which appeared to be the most used ones during the survey. The migration of these developers was then examined for selected thermal papers by migration tests with artificial sweat.

6.1 Provision of thermal paper

6.1.1 Product selection

In recent years, retail has put great focus on the employees' exposure to BPA from point-of-sale receipts, which has entailed a considerable awareness and decisions as to the use of thermal paper for this purpose, cf. information obtained during the mapping. The literature primarily provides knowledge of thermal paper used in point-of-sale receipts (as described earlier), and on the Danish market, no technical tests of material types other than point-of-sale receipts have been carried out.

For the above reasons, it was chosen to focus on uses other than point-of-sale receipts in this project; uses, which typically involve other material types, including thicker qualities and possible back or top coating, as well as other uses and, thus, other exposure scenarios. The obtained products are chosen so that the following areas are represented:

- logistics (self-adhesive labels for sending parcels)
- food labels for weigh-it-yourself items (self-adhesive)
- entry tickets to amusement parks, cultural events, etc.
- transport (tickets for parking, trains, busses, etc.).

All above-mentioned areas are represented with several products, which also ensures variation between the material types.

6.1.2 Collection of products

A total of 30 products (TABLE 5) were purchased or obtained from Danish suppliers and users of thermal paper. All were tested if actually being thermal paper (see section 6.2), and among the confirmed thermal paper products, 24 were selected for analysis of BPA, BPS, BPS-MAE, TGSA, Pergafast 201 and D-8 content, as per the same criteria described above. All 30 products are listed in TABLE 5 stating material type (self-adhesive, paper or cardboard/carton) and use, and it is indicated, whether they are selected for analysis.

The products are obtained between July 14, 2018 and August 8, 2018. Products 1-9 are obtained/purchased from Danish suppliers of thermal paper. Products 10-30 are obtained from Danish users of thermal paper.

TABLE 5: An overview of all products, indicating which ones have been selected for analysis.

Product number	Material type	Use	Analysis
1	Self-adhesive thermal paper	Label	X
2	Self-adhesive thermal paper	Label	X
3	Self-adhesive thermal paper	Label	X
4	Self-adhesive thermal paper	Label	
5	Cardboard/carton	Invitation card/ticket	X
6	Self-adhesive thermal paper	Parcel label	X
7	Self-adhesive thermal paper	Parcel label	X
8	Self-adhesive thermal paper	Parcel label	
9	Self-adhesive thermal paper	Parcel label	
10	Paper	Bus ticket	X
11	Self-adhesive thermal paper	Self-service label: Pick 'n' mix sweets	X
12	Self-adhesive thermal paper	Self-service label: Weigh-it-yourself fruit and vegetables	X
13	Self-adhesive thermal paper	Self-service label: Pick 'n' mix sweets	X
14	Cardboard/carton	Entry ticket	X
15	Cardboard/carton	Gift card, cinema	X
16	Cardboard/carton	Cinema ticket	X
17	Self-adhesive thermal paper	Parcel label	X
18	Self-adhesive thermal paper	Parcel label	
19	Cardboard/carton	Train ticket	X
20	Paper	Paper for penalty tickets	X
21	Paper	Bus ticket	X
22	Paper	Parking ticket	X
23	Cardboard/carton	Train ticket	X
24	Cardboard/carton	Train ticket	
25	Paper	Ferry ticket	X
26	Self-adhesive thermal paper	Parcel label	X
27	Self-adhesive thermal paper	Parcel label	X
28	Self-adhesive thermal paper	Parcel label	
29	Self-adhesive thermal paper	Parcel label	X
30	Self-adhesive thermal paper	Parcel label	X

6.2 Developers in thermal paper

When thermal paper is heated, a chemical reaction is induced between a developer and another component contained in the paper, as a proton is transferred from one molecule to another. This proton transfer to another component affects the component in such a way that a large conjugated system of electrons is created in the molecule. The colour that emerges when heating the paper is a result of this conjugated system, which is illustrated in the below figure (Björnsdotter et al., 2017b):

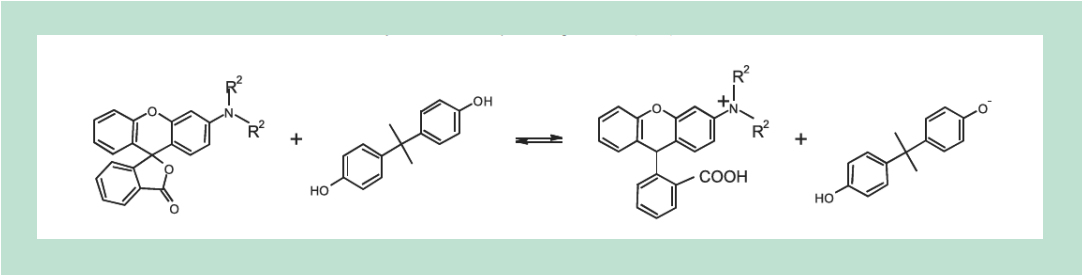


FIGURE 4: Reversible reaction between BPA and leuco dye. Source: Illustration from Björnsdotter et al. (2017b).

Initially, the performance of all obtained thermal papers was tested by heating the paper to 140 °C to develop print on the paper. It turned out that two out of 30 thermal papers (products No. 18 and 28) were not affected by the heating. These two papers are therefore not further analysed for developer content.

6.3 Identification and content analyses of developers

A total of 24 thermal paper products were analysed for content of six specific developers.

6.3.1 Analytical method

A subsample was weighed precisely, measured on one side and segmented. The subsample was extracted with methanol at 60 °C overnight (approx. 16 hours). The extract was then diluted and analysed by high-performance liquid chromatography coupled to a UV detector (HPLC-UV) tuned to optimal wavelengths for the specific components. The method uses a C18-type column and an eluent system consisting of water and acetonitrile.

A component-specific calibration is used for the analysed substances. Standard addition is performed for selected extracts for recovery determination. In addition, all products are analysed in duplicate.

Limit of detection: 10 mg/kg or below the equivalent of 0.001 % (mass)
Limit of quantification: 50 mg/kg or below the equivalent of 0.005 % (mass)
Uncertainty of analysis: 10-15 %

The method used follows a scientific article by Biedermann et al. (2010). In a more recent review article by Björnsdotter et al. (2017b), the methodology for extraction and separation is confirmed in other, more recent scientific articles.

6.3.2 Results

Results are shown in TABLE 6. One developer was found in each of the products. Moreover, traces of a developer other than the primary were also found in almost one third of the products. The results of the content analyses of the various developers correspond with content analyses in earlier studies, which are summarised in TABLE 2. Since a developer has been found in each product, there is no reason to believe that the analysed products contain other developers, which are not included in the analyses.

One developer, Pergafast 201, was not found in the examined products and is therefore not included in TABLE 6. It is uncertain why this developer is not found in the products, which are obtained on the Danish market, despite information found in the survey indicating that products with Pergafast 201 are on the rise and exist in a substantial proportion of the products. One hypothesis can be that this developer is used in other types of products (e.g. point-of-sale receipts) than the ones chosen as focus in this test.

The most frequent developer is BPA, which is found in almost one half of the analysed thermal papers, which is in line with the information in chapter 5 about this developer being frequently used.

From the content analyses, a picture emerges that BPA is used in several types of thermal paper, whereas there is a preponderance of D-8 in stronger quality products (cardboard/carton). No clear picture is observed for self-adhesive labels, but there is an indication of TGSA and BPS-MAE being used in food-related thermal paper, whereas BPA is primarily used in thermal paper for parcel labels. As described in the mapping, the BPS developer is expected to be used in a significant number of samples, but is here only found in one sample (product no. 22), which also stands out from the other products by being paper material instead of cardboard/carton and self-adhesive labels.

TABLE 6: Result of content analyses of developers in selected thermal papers.

	Total content per mg/kg					Total content per unit area [µg/cm^2]				
Product No.	BPS	BPA	BPS-MAE	D-8	TGSA	BPS	BPA	BPS-MAE	D-8	TGSA
1	85	-	12000	-	-	0.7	-	100	-	-
2	-	8600	-	-	-	-	75	-	-	-
3	-	9800	-	-	-	-	85	-	-	-
5	-	-	-	5300	-	-	-	-	95	-
6	-	5700	-	-	-	-	46	-	-	-
7	-	-	-	-	9800	-	-	-	-	88
10	-	9100	-	-	-	-	49	-	-	-
11	-	-	-	-	10000	-	-	-	-	88
12	56	-	8000	-	-	0.5	-	75	-	-
13	-	-	-	-	9200	-	-	-	-	74
14	-	-	-	3600	-	-	-	-	66	-
15	15*	23*	-	6400	-	0.3*	0.4*	-	113	-
16	-	-	-	3500	-	-	-	-	61	-
17	-	8800	-	-	-	-	76	-	-	-
19	-	10000	-	11*	-	-	135	-	0.2*	-
20	-	11000	-	-	13*	-	76	-	-	0.1*
21	-	12000	-	-	-	-	77	-	-	-
22	7600	-	-	-	-	56	-	-	-	-
23	50	-	-	16000	-	0.4	-	-	125	-
25	-	9500	-	-	-	-	66	-	-	-
26	-	9100	-	-	-	-	80	-	-	-
27	24*	-	-	8800	-	0.2*	-	-	79	-
29	-	-	-	-	11000	-	-	-	-	101
30	-	6500	-	-	-	-	52	-	-	-

- means that the result is below the limit of detection (10 mg/kg).
* means that the result us below the limit of quantification (50 mg/kg).

6.4 Migration tests

Thermal paper has a sandwich structure, in which there can be a top coating on top. This sandwich structure is illustrated in FIGURE 1 from Christensen et al. (2014). Then there is a thermal reactive layer, in which developer and dye are present. At the bottom is the precoat

layer and the structural element, made of either paper or polymer. Depending on how the thermal paper is structured, the risk of exposure to developers can vary. This risk of exposure can be examined by a migration test.

Six products were examined for migration of four developers: BPS, BPS-MAE, D-8 and TGSA. Two different exposure durations were used. Based on earlier projects carried out by Christensen et al. (2014) and Lassen et al. (2011), an exposure duration of 5 seconds was chosen. In addition, several migration tests were carried out with an exposure time of 1 minute, with the purpose of examining developer migration over time, as migration of the chosen developers only has been examined to a limited extent. Furthermore, migration over time affects the risk assessment of these BPA alternatives.

6.4.1 Migration conditions

Samples were weighed and immersed in preheated artificial sweat (37 °C), which is also used in DS/EN ISO 105-E04. The ratio between the area of one surface of the sample and the volume of the artificial sweat was 1.5 cm^2/mL, corresponding to 0.01-0.03 g/mL, depending on the sample material. It was ensured that the whole surface was exposed to the simulant. The sample was not shaken during the immersion or migration.

The migration fluid applied was artificial sweat, which is described in DS/EN ISO 105-E04. It consists of 1-histidine-monohydrochloride-1-hydrate, sodium chloride, sodium dihydrogen phosphate and sodium hydroxide for adjustment of pH to pH 5.5.

After homogenisation treatment of the artificial sweat, 1 mL was taken after the established exposure time for the test. The subsamples were filtered before analysis with reverse phase HPLC coupled to a UV detector. Parameters for HPLC are as described in the content analysis. Each product was analysed in duplicate for each exposure time.

Limit of detection: 10 mg/kg or below the equivalent of 0.001 % (mass)
Limit of quantification: 50 mg/kg or below the equivalent of 0.005 % (mass)
Total uncertainty of analysis: 15-25 % for migration and analysis

6.4.2 Results

Results of the migration tests are shown in TABLE 7 and TABLE 8. Results of the content analyses are included for comparison.

Migration of developers has been observed in three out of six products. However, it is only with the 1-minute exposure duration that these results can be reported above the limit of quantification. The highest migration is observed for product number 22. This product stands out from the rest of the products as the material type is paper (TABLE 5) and the developer is BPS. The rest of the tested products are made of stronger material, such as cardboard/carton. However, there is no knowledge of a possible back or top coating on the thermal paper, which can affect the degree of migration. A stronger material type (and possibly back or top coating) can affect migration of a developer, in that the developer can be better contained. That the migration is significantly higher for product no. 22 can therefore not necessarily be ascribed to the developer, which is BPS.

The migrated amount of developer relative to the total content in the product is shown in brackets for the mean result.

TABLE 7: Result of migration tests of developer relative to weight.

		Total content**	Migration after 5 sec.		Migration after 1 min.	
Product No.	**Developer**	**[mg/kg] mean**	**[mg/kg]**	**[mg/kg] mean**	**[mg/kg]**	**[mg/kg] mean**
11	TGSA	10000	16* 23*	19* (0.19%)	95 98	96 (0.98%)
12	BPS-MAE	8000	- -	-	- -	-
13***	TGSA	9200	-	-	n.a.	n.a.
16	D-8	3500	22* 29*	26* (0.75%)	140 120	130 (3.7%)
22	BPS	7600	1600 1400	1500 (20%)	1900 2200	2100 (27%)
23	D-8	16000	- -	-	n.a. n.a.	n.a.

- means that the result is below the limit of detection (10 mg/kg).
n.a. means not analysed.
* means that the result is below the limit of quantification (50 mg/kg).
** results from TABLE 6.
() the figure in brackets is the amount of developer which has migrated relative to the total content.
*** due to a limited amount of test material, only single determination has been performed for the migration.

TABLE 8: Result of migration tests of developer relative to surface area.

		Total content**	Migration after 5 sec.		Migration after 1 min.	
Product No.	**Developer**	**[µg/cm²] mean**	**[µg/cm²]**	**[µg/cm²] mean**	**[µg/cm²]**	**[µg/cm²] mean**
11	TGSA	88	0.13* 0.21*	0.17* (0.19%)	0.84 0.87	0.86* (0.98%)
12	BPS-MAE	75	- -	-	- -	-
13***	TGSA	74	-	-	n.a.	n.a.
16	D-8	66	0.40* 0.51*	0.46* (0.75%)	2.4 2.2	2.3* (3.7%)
22	BPS	56	13 10	11* (20%)	14 17	16* (27%)
23	D-8	125	- -	-	n.a. n.a.	n.a.

- means that the result is below the limit of detection (0.07 µg/cm^2).
n.a. means not analysed.
* means that the result is below the limit of quantification (0.35 µg/cm^2).
** results from TABLE 6.
*** due to a limited amount of test material, only single determination has been performed for the migration.

For product no. 22, a large variation is seen by duplicate determination for migration tests, which is also reflected in the fact that discoloration of the migration fluid is observed already after 5 seconds. Therefore, there is a significantly higher uncertainty associated with the migration tests for this product.

6.5 Summary and conclusion of chemical analyses

One developer was identified in all thermal papers by content analyses. The content is reported and has turned out to represent a value corresponding to 0.4-1.6 weight percent. This is in line with the expectations. The developer Pergafast 201 was not found in any of the selected products, and, thus, the content analyses do not support the information from the survey about Pergafast 201 being used on the Danish market. However, this can be caused by the fact that Pergafast 201 is not used in the specific types of thermal paper included in the analyses.

Since one out of the six developers has been found in all products, there is no reason to believe that there are other developers not included in the analyses in any of the selected products.

Unlike the study from 2017 (Björnsdotter et al., 2017b), no products were found containing a mixture of developers. In a few cases, BPS was found at a concentration level of 0.01 weight percent. This is probably because BPS is a chemical impurity to the stated developer. Traces of BPA, D-8 and TGSA were also observed.

The migration tests of selected thermal papers include four different developers. These developers represent alternatives to BPA. At the same time, the selected products are made from different materials, which vary from self-adhesive material with a shiny surface to strong cardboard material. The diversity in product materials can significantly affect the migration of the constituents. The results of migration tests for different developers are therefore not directly comparable.

The material type has a significant importance for the fragility of the product when it is subjected to fluids. Already 5 seconds into the migration tests, it was observed that paper in the form of a parking ticket (product no. 22) discoloured the migration fluid. This indicates that the paper begins to decompose. In this case, the identified developer was BPS. Results for both the content analysis and migration tests for this product seems to be comparable with analyses performed for thermal paper with BPS in an earlier report by Christensen et al. (2014), which found that approx. 10% BPS migrated after five seconds from a point-of-sale receipt with 1.0 % developer.

The results of the migration tests for the three developers TGSA, BPS-MAE and D-8 show far less or no migration compared to the BPS result. However, this can not necessarily be ascribed to the developer type, as the material type can significantly affect the developer migration. For three products, no migration is seen after 5 seconds, and a single product (product no. 12) is also tested with an exposure duration of 1 min., in which case the developer, likewise, could not be detected. For these products, where there is low or no migration, the material type is either self-adhesive paper with a coated surface or cardboard/carton. These material types have a stronger construction in common, which can contribute to enhanced durability of the product, but also a better containment of the developers. Better containment means less migration of developers.

7. Risk assessment

In this chapter, the results from migration analyses are used to create exposure scenarios and determine the exposure for alternative developers of a consumer, who gets into contact with the label/ticket.

Then, the available data on the toxicological effects of the migrated developers are reviewed, where the most critical effects related to skin contact are stated, and tolerable exposure levels (DNEL values) of these effects are calculated, wherever possible.

Finally, the calculated exposure of consumers is compared to the tolerable exposure levels to assess, whether the exposure to the alternative developers constitutes a health risk. Additionally, a final assessment of uncertainties and limitations is determined regarding the exposure, hazard assessment as well as the risk assessment.

7.1 Exposure assessment

The assessment is based on findings in migration analyses shown in TABLE 7 and 8, where migration of TGSA (from a self-adhesive paper label for pick n' mix candy bag), D8 (from a cardboard/carton cinema ticket) and BPS (from a paper parking ticket) was detected.

The following assumptions mentioned below are used for the creation of an exposure scenario for these three types of tickets, since the point of departure are assumptions that are considered being realistic worst-case scenarios.

It can be mentioned that the ECHA/RAC (2015) assessment of limitation proposal for the usage of BPA in point-of-sales receipts determined that the duration for skin absorption of BPA from point-of-sales receipts was up to 2 hours per day for a consumer.

Self-adhesive labels for pick n' mix candy bag, TGSA

Here, a child of approx. 6 years of age, who is sitting and watching a movie with a candy bag in her hands, is considered the most exposed, given the assumption of an exposure time of 2 hours, where a child holds a candy bag in sweaty hands.

The migration results show that TGSA within 1 minute is only emitted in a relatively limited amount of 0.86 µg TGSA/cm^2 (or 0.98% of label's TGSA-content per cm^2), when the label is submerged and soaked in artificial sweat. It is, thus, possible to assume that a larger volume would be emitted over a 2-hour period, even if the label is only moistened with hand perspiration. Over a period of 2 hours, it is, thus, determined that 10% corresponding to 8.8 µg TGSA/cm^2 is available for skin exposure. Uncertainties are related to this estimate, but it is considered unrealistic that much more than 10% is emitted, since the label would not be entirely soaked with sweat and TGSA is also to some extent bound to the paper. On the other hand, the measured value after 1 minute is too low, because an exposure time with skin contact of 2 hours should be taken into consideration.

By calculation of the exposure the following is assumed:

Child's body weight, 6 years: 23 kg (RIVM 2006)
Exposure duration: 2 hours (120 minutes)
Label surface: 30 cm^2 (measured)
Emission from label per cm^2: 8,8 µg TGSA/ cm^2

Exposure = 30 cm^2 (area) x 8,8 µg TGSA/ cm^2 / 23 kg = 11 µg TGSA /kg lgv /d

Cinema ticket, D-8
Here, a child of approx. 6 years of age, who is sitting and watching a movie while fiddling/playing with the cinema ticket with sweaty hands. Again it is assumed that the exposure time is 2 hours.

The migration results show that within 1 minute D-8 is only emitted to a certain volume with 2.3 µg D-8/cm^2 (or 3.8% of the content per cm^2) if the label is submerged or soaked in artificial sweat. Thus, it is possible to assume that a larger volume would be emitted over a 2-hour period, even if the label is only moistened with hand perspiration. Over a period of 2 hours, it is thus determined that 20% corresponding to 12 µg D-8/cm^2 is available for skin exposure. Uncertainties are related to this estimate, but it is considered unrealistic that much more than 20% is emitted, because the label would not be entirely soaked with sweat. On the other hand, due to migration results the value for D-8 is assessed higher than for TGSA, which is why the value is estimated to be 20%.

By calculation of the exposure the following is assumed:

Child's body weight: 6 years: 23 kg (RIVM 2006)
Exposure duration: 2 hours (120 minutes)
Label surface: 48 cm^2 (measured)
Emission from label per cm^2: 12 µg D-8/ cm^2

Exposure = 48 cm^2 (area) x 12 µg D-8/ cm^2 / 23 kg = 25 µg D-8/kg lgv /d

Parking ticket, BPS
Here, an adult woman (due to lower body weight than men) is assumed to be exposed the most. A worst-case scenario here is a ticket that lies in the pocket, and the woman is unknowingly fiddling with the ticket while she watches e.g. a movie. It is assumed that the exposure time is 30 minutes.

The migration results show that within 1 minute BPS is emitted in relatively large volume with 16 µg BPS (or 29 % of the content per cm^2) if the label is submerged or soaked in artificial sweat. Thus, it is possible to assume that a larger volume would be emitted over a 30-minute period, even if the label is only moistened with hand perspiration. Over a period of 30 minutes, it is thus determined that 50% or 28 µg BPS/cm^2 is available for skin exposure. Uncertainties are relate to this estimate, but it is considered unrealistic that much more than 50% is emitted, because the label would not be entirely soaked with sweat. On the other hand, due to migration result the value for BPS is assessed higher (and migration is faster) than for TGSA, which is why the value is estimated to be 50%.

By calculation of the exposure the following is assumed:

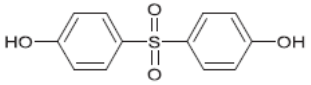
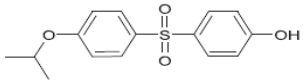
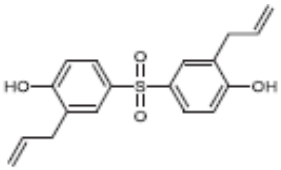
Woman's body weight: 60 kg
Exposure duration: 30 minutes
Label surface: 55 cm^2 (measured)
Emission from label per cm^2: 28 µg BPS/ cm^2

Exposure = 55 cm^2 (area) x 23 µg BPS/ cm^2 / 60 kg = 26 µg BPS/kg lgv /d

7.2 Hazard assessment

Based on expert assessment described in ECHA (2015) and US EPA (2015), where toxicological data for the alternative developers have been assessed, and based on the data indicated in REACH registrations of these substances, a toxicological profile has been created in Appendix 1 for each of the three BPA alternatives. The most important data from Appendix 1 have been summarized below in TABLE 9 to achieve a complete overview of these data.

TABLE 9. Overview of data for BPS, D-8 and TGSA indicated by ECHA (2015), US EPA (2015) and data from REACH registrations.

	BPS; CAS CAS 80-09-1	D8; CAS 95235-30-6	TGSA; CAS 41481-66-7	Comments
Structure				
Classification (REACH registration)	Repr. 2 H361f	No Human health classification	Skin Sens 1, H317	BPS of most concern
Acute tox Oral, dermal, inh.	Low concern (oral, dermal)	Low concern (oral, dermal, inh)	Low concern (oral, dermal)	Low concern for all three substances
Skin irritation/corrosion	Low concern	Low concern (OECD 404 *in vivo* test)	Low concern (OECD 404)	Low concern for all three substances
Eye irritation/ damage	Low concern	Low concern (EPA OTS 798.4500)	Low concern	Low concern for all three substances
Skin sensitisation	Low concern (OECD 429, LLNA test)	Non-conclusive equivocal data	Skin sensitizer (OECD 406, GPMT test)	Degree of concern: TGSA (high) > D8 moderate > BPS (low)
Repeated dose toxicity	NOAEL(oral): 100 mg/kg bw/day OECD 408 (90D, oral, wistar rats) NOAEL: 10 mg/kg bw/day LOAEL: 60 mg/kg bw/day effects on cecum. OECD 421, Fischer rats	NOEL = 10.9 mg/kg bw/day Oral, rat, 28 days study (no details and LOAEL indicated)	NOAEL = 15 mg/kg bw/day LOAEL = 150 mg/kg bw/day, kidney toxicity 28D oral, rats STOT RE2 (kidneys) possibly warranted	Reporting of data on TGSA and especially D8 very poor
Mutagenicity *in vitro*	Negative in bacteria (OECD 471) Negative in mammalian cells (OECD Guideline 476 (*In Vitro* Mammalian Cell Gene Mutation) Negative, chromosme abberation V79 cells (OECD 473) Positive, chromosome abberation CHO cells	Negative in bacteria (OECD 471) and mammalian cells (OECD 473)	Negative in bacteria (OECD 471) and mammalian cells (OECD 473)	Low concern for mutagenicity for any of the three substances

Mutagenicity in vivo	Negative /OECD Guideline 474; Mammalian Erythrocyte Micronucleus Test, mice)	Negative in micronucleus test (OECD 474)	Negative in micronucleus test (OECD 474)	
Cancer	No data	No data	No data	-
Fertility	NOAELparental: 10 mg/kg bw/day NOAELfertility: 60 mg/kg bw/day (OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) OECD 443 (extended one-generation study on-going)	NOAEL = 125 mg/kg bw/day (OECD 415, one-generation study, no further data)	No data US EPA (2015) suggest read-across to data on BPS	Only details on test data for BPS. Data for D-8 and TGSA is lacking.
Developmental toxicity	NOAELmaternal: 100 mg/kg bw/day NOAELdevelopment: 300 mg/kg bw/day (OECD 414 Prenatal Developmental Toxicity Study)	No data	No data US EPA (2015) suggest read-across to data on BPS	Only data on BPS Data lacking for D8 and TGSA.
Endocrine activity	Estrogenic activity shown *in vitro* and *in vivo*	*In vitro,* Negative for estrogenicity and positive for anti-estrogenicity.	Weak estrogenic response *in vitro* and no estrogenic response *in vivo* in utero-trophic assay	Most evidence for BPS. Limited data on D-8 and TGSA
DNEL oral from REACH registration	DNEL, consumer = 0.5 mg/kg bw/day Based on a NOAEL of 100 mg/kg bw/day from the OECD 408 oral, Wistar rat study and applying an overall assessment factor of 200. DNEL dermal = 1 mg/kg bw/day	DNEL, consumer = 0.25 mg/kg bw/day (both for oral and dermal exposure) From the NOAEL of 50 mg/kg bw/day in Wistar rats and by applying an overall assessment factor of 200.	No value indicated	
DNEL oral, consumer for this project	DNEL, consumer= 0.017 mg/kg bw/d Based on a NOAEL of 10 mg/kg bw/day from an OECD 421 oral Fischer rat study and applying an overall assessment factor of 600.	DNEL, consumer = 0.009 mg/kg bw/day Based on a NOEL of 10.9 mg/kg bw/day	DNEL, consumer= 0.025 mg/kg bw/d Based on a NOAEL of 15 mg/kg bw/day from a 28D oral rat study and applying an overall assessment factor of 600.	

	from a 28D oral rat study and applying an overall assessment factor of 1200.

BPS

BPS is the most widely investigated substance out of the three alternative BPA developers. The substance has been classified for adverse effects on fertility with Repr. 2 H361f, since an effect on the estrogen cycle of mother rats, decreased fertility index and reduced number of living offspring was observed by a dosage to mother rats of 300 mg/kg lgv/day in OECD Guideline 421-tests. NOAEL for these effects was at 60 mg/kg lgv/day.

The tests also showed a distension of the appendix in mother rats at 60 mg/kg lgv/day with a NOAEL of these effects at 10 mg/kg lgv/day. A similar effect could be observed in another test with rats. Based on the latter NOAEL value, an oral DNEL value of 0.017 mg/kg lgv/day can be calculated for consumers.

The substance has also been found to have an indication of a hormone-disrupting activity in both *in vitro* and *in vivo* tests.

It can be mentioned that ECHA/RAC (2015) in their assessment of restriction proposal for BPA consider the substance BPS as an alarming alternative, because RAC fears that BPS, due to existing data and the great structural resemblance, has equivalent properties to BPA.

Follow-up data

To supplement with a potentially more recent knowledge, internet-based search on toxicological data has been carried out.

This literature has been reviewed in Appendix 1. Here, specifically the most recent metabolism tests are interesting, as they show high comparability with BPA regarding absorption, metabolism and discharge of the substance. BPS is metabolized just as BPA, especially in the liver, and is converted into coupling products with glucuronic acid and sulphate by one of the terminal -OH groups. These metabolites have been found to be inactive in *in vitro* test for estrogenic activity.

Lastly, publications have been found that substantiate the comparability with BPA regarding adverse effects. In a test, new-born rat offspring were dosed with either BPA and BPS by subcutaneous injection of 0, 0.5 and 50 mg/kg lgv/day. In case of the highest dosage, a reduced number of born offspring was observed. For both substances, the offspring were observed to have a delayed sexual maturity and changed oestrous cycle (highest dosage) as well as an increased weight of the uterus (at two highest dosages). Furthermore, a dosage-related increased occurrence of follicles was observed in ovaries.

Other tests at a very low oral dosage in mice (in the interval of 1-200 µg/kg lgv/day) found an impact on the mammary glands in mother rats and an impact on their behaviour during rearing of the offspring, while oral dosage in male rats at the interval of 1- 50 µg/kg lgv/day for 30 days resulted in morphological changes and reduced testosterone contents in testicle tissue. These tests are complicated to interpret regarding the establishment of a critical dosis as a basis for DNEL calculation, because a more precise documentation of findings is necessary, and the effects in some cases did not occur in a dosis-related context.

Lastly, after dosing mice through feed with 0, 5, 50, 500, or 5000 µg BPS/ kg lgv/day for up to 8 weeks, histopathologic changes in liver and increased plasma levels of alanine aminotransferase, aspartate aminotransferase and total bilirubin (highest dosis) were detected. Since the effects on liver were only reported in rats at very high dosis, the mice are considered to be more sensitive towards this effect, and the relevance of this effect in humans cannot be excluded, which is why a DNEL value is also calculated for this effect. As indicated in Appendix 1, an oral DNEL(II) of 0.0024 mg/kg lgv/day can be calculated based on mice test (see Appendix 1).

It must be mentioned that the calculated oral DNEL(I) of 0.017 mg/kg lgv/day from OECD 421 rat test and the calculated oral DNEL(II) value of 0.0024 mg/kg lgv/day from mice tests is considerably lower than the oral DNEL of 0.5 from REACH registration of the substance, where a NOAEL of 100 mg/kg lgv/day and a total uncertainty factor of 200 have been used as a basis for the calculation.

D-8

Only relatively few data for D-8 can be found, and the existing data are very scarcely and insufficiently reported in the REACH registration. According to the REACH registration, the substance should not be classified as hazardous. The substance has been found not to be skin sensitising in an OECD 406 test (GPMT-test), while it has been found skin sensitising in another test which has not been described in further detail. In two out of three QSAR models applied in the Danish QSAR database, the substance is indicated as being positive for skin sensitisation, which allows to assume that there is a certain risk of this effect. After 28-day oral dosis to Fischer rats, a NOAEL of 10.9 mg/kg lgv/day has been indicated, while in a 90-day test with oral dosis to Wistar rats the NOAEL was 50 mg/kg lgv/day. In a one-generation OECD 415 test, a NOAEL of 125 mg/kg lgv/day was indicated for both the parent generation and the offspring. From *in vitro* tests, there are indications of effects on the estrogenic activity.

No additional data for D-8 were found in the internet-based literature search.

Based on a NOAEL value of 10.9 mg/kg lgv/day, an oral DNEL value of 0.009 mg/kg lgv/day can be calculated for consumers (see Appendix 1).

TGSA

Only relatively few data are available for TGSA. The substance has been found to be skin sensitising in an OECD 406 test (GPMT-test) and has been classified with Skin. Sens 1. After 28-day oral dosis to rats, changes in kidney tissue have been detected at 150 mg/kg lgv/day with a NOAEL of 15 mg/kg lgv/day.

ECHA (2015) states that this should possibly require a classification with STOT RE 2, H373 (kidneys). No data are available regarding the effects of this substance on the reproductive ability or the feto-toxic effects of this substance. Signs of a weak estrogenic activity in *in vitro* tests have been observed, while these could not be retrieved in *in vivo* tests.

No additional data for TGSA were found in the internet-based literature search.

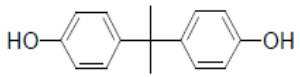
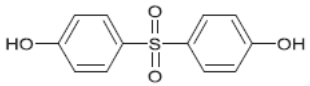
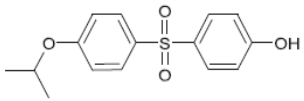
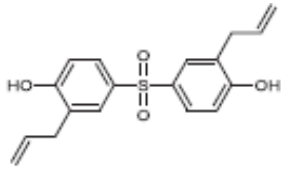
Based on a NOAEL value of 15 mg/kg lgv/day, an oral DNEL value of 0.025 mg/kg lgv/day can be calculated for consumers (see Appendix 1).

Dermal DNEL values for the alternative developers

To carry out a risk assessment on skin exposure from labels, it is necessary to calculate a DNEL value for skin contact. When a DNEL for skin contact is calculated based on a DNEL value for oral exposure, it is necessary to consider the differences in the absorption of the substance in relation to oral and dermal exposure (ECHA, 2012). The assessment of the degree of skin absorption requires a comparison of substance with the structurally related BPA, and for which ECHA (2015), US EPA (2015) and EFSA (2015) determine a dermal absorption of 10% according to concrete data.

TABLE 10 below shows data that are relevant for the assessment of skin absorption and the conversion from oral to dermal exposure.

TABLE 10. Physicochemical data, skin absorption data and oral ingestion of BPA and alternatives.

	BPA; CAS-No. 80-05-7	BPS; CAS-No. 80-09-1	D-8; CAS-No. 95235-30-6	TGSA; CAS-No. 41481-66-7
Structure				
Water solubility US EPA (2015)	120 – 301 mg/L (measured values)	1100 mg/L (measured)	19.7 mg/L; 21 mg/L (measured values)	4.79 mg/L (measured)
Log Kow US EPA (2015)	2.2; 3.32 (measured values)	1.2 (measured)	3.36 (measured)	3.22 (measured)
Dermal absorption				
US EPA (2015) Dermal absorption	10 %; (measured interval 3 – 11.4%)	None specified	Low skin absorption in dissolved form	Low skin absorption in dissolved form
ECHA/RAC (2015) Dermal absorption	10 %	No data	No data (referring to US EPA 2015)	No data (referring to US EPA 2015)
Dermal absorption (Danish QSAR database, EPI Derwin modelling)	0.00683 mg/cm^2	0.00933 mg/cm^2	0.00216 mg/cm^2	None specified
REACH registration	1.7 – 13 % *in vitro* data	OECD Guideline 428 (Skin Absorption: In Vitro Method) 8.79 %	100%*	No data
Estimated dermal absorption	10 %	10 %	3 %	3 %
Oral absorption				
ECHA (2015) Oral absorption	> 85 % (3 %)	-	-	-
Oral absorption (Danish QSAR database, EPI Derwin modelling)	100 %	90 %	100 %	No data

*No data; the percentage is based on the relationship DNEL oral / DNEL dermal

For BPS, an *in vitro* test for skin absorption is available that indicates an absorption at 8.79%. This is highly comparable with data for BPA, which is why in this report the same degree of absorption for BPS will be applied as indicated for BPA, i.e. skin absorption of 10%.

No data are available for D-8 and TGSA. US EPA (2015) rates the skin absorption of these substances as very low, and in the EPI Derwin model calculations indicated in the Danish QSAR database, the skin absorption is calculated to be more than 3 times lower for D-8 than for BPA. According to this, a skin absorption of 3% is assumed for both D-8 and TGSA.

Two methods will be applied for the conversion from oral DNEL to dermal DNEL. For the initial, more conventional method, the relation between oral and dermal absorption is included, i.e.:

DNEL dermal = DNEL oral x oral absorption/ dermal absorption

This leads to:

BPS: DNEL(I) dermal = 0.017 mg/kg lgv/day x 90% / 10% = 0.153 mg/kg lgv/day
DNEL(II) dermal = 0.0024 mg/kg lgv/day x 90% / 10% = 0.022 mg/kg lgv/day

D-8**:** DNEL dermal = 0.009 mg/kg lgv/day x 100% / 3% = 0.30 mg/kg lgv/day

TGSA: DNEL dermal = 0.025 mg/kg lgv/day x 100% / 3% = 0.83 mg/kg lgv/day

For TGSA, no values for absorption have been indicated. Thus, due to the largest comparability with D-8 as to water solubility and log K_{OW}, the same values as for D-8 are used.

Using the other method, it is assumed that for the alternative developers, just as for BPA despite the high absorption in abdomen-intestines, a large first-pass metabolism of the substance in the liver takes place, because one of the terminal -OH groups in the BPA molecule are conjugating with glucuronic acid or sulphate and are thus deactivated, so that only approx. 3% of the injected dosis is actually absorbed in the organism. In relation to the restriction proposal for BPA, EHCA/RAC (2015) convert an oral DNEL to a dermal DNEL, since they apply a pharmacokinetic model calculation for the conversion from dosis in animal tests to human dosis, and where they pay attention to the high first-pass metabolism in liver.

The results of calculations from an oral DNEL value of 4 µg/kg lgv/day results in a DNEL value of 0.1 µg/kg lgv/day for internally absorbed human dosis at dermal exposure, i.e. DNEL for internal dosis after skin contact is *40 times lower* than the oral DNEL value, because the first-pass metabolism is avoided in case of dermal exposure.

With a dermal absorption of 10% for BPA, this corresponds to an external dermal dosis
of 1 µg/kg lgv/day, i.e. that the dermal external DNEL is lower than the oral DNEL at 4 µg/kg lgv/day. In other words, the BPA is relatively more toxicologically potent at skin contact compared to oral exposure.

If the same conditions are assumed to be valid for the alternative developers with terminal -OH groups, which can be conjugated and deactivated by coupling to glucuronic acid and sulphate, the dermal DNEL internal values are correspondingly lower than the oral DNEL values for these developers. However, no data are available for these conditions, but if a factor 40 is also applied together with the oral DNEL values for alternatives, the following is achieved:

BPS
DNEL(I) internal dosis, dermal = DNEL(I) oral x 4* / 40 = 0.017 mg/kg lgv/d x 4* / 40 = 0.0017 mg/kg lgv/d
If 10% skin absorption is taken into consideration, this will lead to an external dermal DNEL value of:
DNEL(I) dermal = 0.0017 mg/kg lgv/d x 90% / 10% = 0.015 mg/kg lgv/d

or

DNEL(II) internal dosis dermal = DNEL(I) oral x 7* / 40 = 0.0024 mg/kg lgv/d x 7* / 40 = 0.0004 mg/kg lgv/d

If 10% skin absorption is taken into consideration, this will lead to an external dermal DNEL value of:
DNEL(II) dermal = 0.0004 mg/kg lgv/d x 90 % / 10 % = 0.0036 mg/kg lgv/d

D-8
DNEL internal dosis, dermal = DNEL oral x 4* / 40 = 0,009 mg/kg lgv/d x 4* / 40 = 0.0009 mg/kg lgv/d

If 3% skin absorption is taken into consideration, this will lead to an external dermal DNEL value of:
DNEL dermal = 0.0009 mg/kg lgv/d x 100% / 3 % = 0.03 mg/kg lgv/d

TGSA
DNEL internal dosis, dermal = DNEL oral x 4*/ 40 = 0.025 mg/kg lgv/d x 4*/ 40 = 0.0025 mg/kg lgv/d

If 3% skin absorption is taken into consideration, this will lead to an external dermal DNEL value of:
DNEL dermal = 0,0025 mg/kg lgv/d x 100 % / 3 % = 0.08 mg/kg lgv/d

*Since the method using a factor 40 is based on toxicokinetic calculations, it must be noted that when converting from the oral DNEL value one must be aware that when calculating the latter an allometric scaling factor (kinetic factor) as already been applied, which is why this factor must be deducted. The allometric scaling factor between rats and humans is at 4 and between mice and humans – factor 7 (see calculation for oral DNEL values in Appendix 1).

This means that depending on whether a first-pass metabolism occurs (as it is seen for BPA) or not, very different DNEL values are achieved for the dermal exposure (TABLE 11).

TABLE 11. Dermal DNEL values for BPS, D-8 and TGSA calculated conventionally and taking a decreased metabolism into account.

	BPS	D-8	TGSA
DNEL dermal (conventional method)	0.15 mg/kg lgv/day (I) 0.022 mg/kg lgv/day (II)	0.30 mg/kg lgv/day	0.83 mg/kg lgv/day
DNEL dermal (decreased metabolism)	0.015 mg/kg lgv/day (I) 0.0036 mg/kg lgv/day (II)	0.03 mg/kg lgv/day	0.08 mg/kg lgv/day

In the table, DNEL values, when it is possible to include first-pass metabolism, is 10 times lower than DNEL values calculated with the conventional method.

7.3 Risk assessment

7.3.1 Risk characterisation

TABLE 12 below provides an overview of the calculated exposure values for three alternative developers with their respective tolerable exposure levels (i.e. DNEL values), and risk characterisation ratio (RCR = exposure / DNEL).

TABLE 12. Risk assessment (RCR-calculation) of exposure scenarios for BPS, D-8 and TGSA.

	Calculated dermal exposure mg/kg/day	DNELdermal (conventional) mg/kg lgv/day	RCR (conv.)	DNELdermal (decreased metabolism) mg/kg lgv/day	RCR (decreased metabolism)
TGSA, pick n' mix candy bag label, child	0.011	0.83	***0.01***	0.08	***0.14***
D-8, cinema ticket, child	0.025	0.30	***0.08***	0.03	***0.83***
BPS, parking ticket, adult	0.026	0.15 (I) 0.022 (II)	***0.17(I)*** ***1.2(II)***	0.015 (I) 0.0036 (II)	***1.73(I)*** ***7.2(II)***

TGSA and D-8
When calculating RCR using conventionally calculated DNEL values and calculations where DNEL (decreased metabolism) is applied, RCR values are obtained in the interval 0.03 to 0.83 for D-8 and TGSA, which is why no health-related risks related to these scenarios can be detected.

However, it should be underlined that TGSA is skin sensitising, while D-8 is suspected being skin sensitising. For this effect, it is not possible to calculate a DNEL value as it is highly complicated to establish a threshold value for skin allergy and requires a range of data. Thus, skin contact with these substances should be entirely avoided not to risk the development of a skin allergy. Here, particularly a long-term contact with sweaty hands should be avoided.

BPS
Here, the risk assessment based on DNEL (decreased metabolism) is regarded as more relevant than the application of DNEL using the conventional method, as data indicate that BPS is metabolised and deactivated in the same way as BPA. For the calculated DNEL values, where metabolism is considered, RCR values are obtained at 1.7 and 7.2, which indicates an unacceptably increased risk. However, this should be seen in the light of the mentioned uncertainties and limitations described below.

As to BPA in point-of-sales receipts, ECHA/RAC (2015), based on a far greater amount of data, calculated the RCR value at 0.5 for consumers assuming 10% skin absorption of emitted BPA. The restrictions of BPA in point-of-sales receipts is, thus, primarily substantiated by the exposure of point-of-sales employees, where RCR was calculated up to value 7.

7.3.2 Uncertainties and limitations

Exposure assessment
The exposure considerations involve a rather high uncertainty, since they are based on migration data after 1 minute, where the label/ticket has been entirely submerged into artificial sweat, while the exposure scenario includes up to 2-hour skin contact with sweaty hands. It is, hence, unknown, how migration proceeds after the first minute, which is why it is estimated that a certain percentage (percentage of the volume of 1-minute migration values) of the total amount of developers can migrate within these two hours. The percentage is considered a worst-case situation, but it is naturally subject to uncertainty. Further, it is assumed that the entire migrated amount is available for skin absorption, and that there is constant contact

with sweaty hands. In general, the exposure scenarios are based on assumptions that will overestimate the exposure, which is why RCR values that are slightly above value 1 are considered not to constitute a risk.

Hazard assessment
The missing data for these three substances and specifically D-8 and TGSA means that DNEL values are established with a relatively high uncertainty. In particular, an incomplete report of the few data available for D-8 and TGSA limit the assessment foundation for DNEL calculations. It is, hence, not uncommon that the more data that are obtained for a substance, the lower the effect levels and DNEL values are obtained. This can particularly be observed for BPA in line with the increased knowledge about the substance.

For substances D-8 and TGSA, no data are available on the first-pass metabolism of the substances, which is why additional data are required to be able to apply the truest method for risk assessment of these substances.

The data for BPS regarding the metabolism of substances indicate a high comparability with BPA, which means that the risk assessment method, where the first-pass metabolism of the substance in the liver is taken into account, is the most relevant method.

However, the uncertainty for establishing the truest DNEL for BPS, as data in low-dosis areas are very intricate to interpret (which is also the case for expert statements on low-dosis effects of BPA), and the two dermal DNEL calculations shown in this report vary with factor 5.

7.3.3 Conclusion

This report contains limited data for the substances TGSA, D-8 and BPS related to migration from thermal paper (a single set of test data for each substance). This, together with uncertainties in both exposure estimates and DNEL calculations, does not provide a foundation for representative risk assessment conclusions on the usage of thermal paper. Even for the concrete product assessments mentioned above, the uncertainties are too great regarding the exposure and DNEL estimates to allow for a clear conclusion.

Even with the most critical method, the scenarios for the three concrete labels/tickets cannot be assessed to cause a risk of systemic effects, because the exposure assessment should be seen as a worst-case scenario and the exposure only occurs on an occasional basis. Hence, RCR values slightly above the value 1 cannot be considered to constitute an unacceptable risk.

The increased knowledge about the harmful effects of BPS strengthens the assumption of BPS having harmful effects similar to those of BPA. The use of alternatives with allergenic properties may be considered worrying in products with skin contact, e.g point-of-sales receipts, since the migration risk must be considered problematic.

This report indicates that increased and more systematic knowledge of the harmful effects of the alternative substances and their migration from point-of-sales receipts is needed to obtain a basis for more accurate risk assessments.

8. Abbreviations

BPA	bisphenol A
BPS	bisphenol S
BPS-MAE	bisphenol S mono-allyl ether
Chemsec	International Chemical Secretariat
CEPI	Confederation of European Paper Industries
CLP	classification, labelling, packaging
CMR	carcinogen, mutagen, reprotoxic
ECHA	European Chemicals Agency
EFSA	European Food Safety Authorisation
ETPA	European Thermal Paper Association
DNEL	derived no effect level
HPLC	high performance liquid chromatography
LOAEL	lowest observed adverse effect level
NOAEL	no observed adverse effect level
Repr.	toxic for reproduction
SVHC	substance of very high concern
TGSA	bis(3-allyl-4-hydroxyphenyl) sulfone
EPA	Environmental Protection Agency
UU	urea-urethane
UV	ultraviolet

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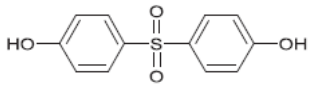
Appendix 1. Toxicological assessment of BPS, D-8 and TGSA

Bisphenol S

In the table below data from the expert assessment provided by US EPA (2015) and ECHA (2015) plus the data from the REACH-registration of the substance is gathered for generating an overall toxicological profile of the substance

TABLE 13. Bisphenol S; CAS 80-09-1, classification (REACH registration): Repr. 2 H361f

Structure 	**I** **REACH registration September 2018** **Study results** **(study type; reference)**	**II** **US EPA, 2015**	**III** **ECHA, 2015**	**Comments/ conclusion**
Toxicokinetics	8,79% dermal absorption OECD Guideline 428 (Skin Absorption: In Vitro Method)	No data	No data	
Acute tox	LD50 (oral, rat): 2830 mg/kg bw. (≈ OECD 401; unnamed study report 1978)	LD50 (oral, rat) = 2,830 mg/kg (ECHA registration 2011) + Several other references with similar level of acute oral toxicity LD50(dermal rabbit) >19,250 mg/kg	Not mentioned	Low potential for acute toxicity (oral and dermal exposure)
Skin irritation/corossion	No skin irritation (in vitro EpidermTM corrosion/irritation model; unnamed report 2010) No skin irritation n rabbit (in vivo OECD 404 unnamed report 1981)	Slight skin irritant, guinea pig (Eastman Kodak, 1991) Non-irritant, rabbit (Monsanto, 1991) Non-irritant, rabbit (ECHA registration 2011)	Not mentioned	Low potential for skin irritation
Eye irritation/ damage	No eye irritation n rabbit (in vivo OECD 405 unnamed report 1984)	Slightly irritating, rabbit (Eastman Kodak, 1991) Mildly irritating, rabbit (Monsanto, 1991) Nonirritating, rabbit (ECHA registration 2011)	Not mentioned	Low potential for eye irritation
Skin sensitisation	No skin sensitization (in vivo OECD 429 LLNA test, unnamed report 2010)	Negative for skin sensitization, guinea pig (Eastman Kodak, 1991) Negative for skin sensitization, mouse local lymph node assay (ECHA registration 2011)	No data identified	Low potential for skin sensitization
Repeated dose toxicity	NOAEL (oral, male rats): 100 mg/kg bw/day NOAEL (oral, female rats): 300 mg/kg bw/day	NOAEL = 10 mg/kg bw-day LOAEL = 60 mg/kg bw-day for effects on cecum (distension, diffuse hyperplasia of mucosal epithelium) (OECD 421, ECHA registration 2011).	NOAEL at 40 mg/kg/d (critical effects: loss of weight gain, effects on kidneys, increase of the renal weight, proteinuria,	NOAEL = 100 mg/kg bw/day based on OECD 408 90D study

	(OECD 408, 90D (0,100,300,1000 mg/kg bw/day); BASF unnamed report 2014)		acidification and presence of urobilinogen in urines, hyperplasia and caecale distension (≈OECD 407 0, 40, 200 or 1000 mg/kg/d of BPS to rats (6 per dose group) by oral route for 28 days. Study from 1999, ECHA website)	
Mutagenicity *in vitro*	Negative ± S9 (OECD 471 Bacterial Reverse Mutation Assay; unnamed report 1989) Negative ± S9 (OECD 473 (In Vitro Mammalian Chromosome Aberration Test, V79 cells; unnamed report 2017(German CA-report)) Negative ± S9 (OECD Guideline 476 (In Vitro Mammalian Cell Gene Mutation Test; CHO/HGPRT mutation, unnamed report 1990) indicated as a supporting study	Negative ± S9, Ames assay (standard plate) in Salmonella typhimurium strains TA98, TA100, TA1537, TA1535, and TA1538. Negative ± S9, Salmonella/microsome test, S. typhimurium strains TA1535, TA100, TA1537, and TA98. Negative± S9, Ames assay (preincubation) in S. typhimurium strains TA98, TA100, TA1537, and TA1535, and Escherichia coli WP2UVRA Negative ± S9, umu test in S. typhimurium strain TA1335 Negative, mouse lymphoma L5178Y (TK+/TK-) cells Negative± S9, CHO HGPRT mutation assay (Amoco Corp., 1991a; as reported by ECHA 2011) Positive, chromosomal aberrations in CHO cytogenetics assay, without metabolic activation, negative with metabolic activation. Results were obtained in the absence of cytotoxicity (Amoco Corp., 1991b; ECHA registration 2011).	The tests of genotoxicity in vitro are negative, except 2 tests of chromosomal aberration which are positive without metabolic activation. The mammalian erythrocyte micronucleus test realized in vivo in the mouse is negative. CHO cells with and without metabolic activation. Positive without metabolic activation at 500 et 600 µg/ml. Cytotoxicity at 700 µg/ml. Negative without metabolic activation at 125, 250, 500, 750 and 1000 µg/ml. Cytotoxicity at 750 and 1000 µg/ml. (OECD 473; European Chemicals Agency, 1991). Lung cells of Chinese hamster (CHL/IU) with and without metabolic activation. Slightly positive without metabolic activation at 400 µg/ml in continuous treatment of 24 hours. (Office of Environmental Chemicals Safety Environmental Health Japan, 1999)	US EPA: The positive result in the in vitro assay and negative result in the in vivo test suggest an equivocal response and therefore a moderate hazard concern is concluded.
Mutagenicity *in vivo*	Negative (OECD Guideline 474, Mammalian Erythrocyte Micronucleus Test, mice (0, 500,1000,2000 mg/kg bw/day), unnamed report 2010)	Negative, did not produce chromosomal aberrations in vivo in a mammalian erythrocyte micronucleus assay in male NMRI mice (5/group) administered bisphenol S via single gavage dose at	Negative: Male mice NMRI exposed by gavage (500, 1000, 2000 mg/kg), then sacrificed 24h after (and 48h after in the group at 2000 mg/kg). Test realized on bone marrow.	

		dose levels up to 2,000 mg/kg (ECHA registration 2011)	(European Chemicals Agency, 2010)	
Cancer	No data	Using OncoLogic expert system indicates a moderate for a potential carcinogenesis or tumorigenesis promoter arising from its structural similarity to estrogenic/androgenic compounds, using the "phenols and phenolic compounds" structural alert.	No data	Non-conclusive
Fertility	NOAELparental: 10 mg/kg bw/day NOAELfertility: 60 mg/kg bw/day (OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test. 0,10,60,300 mg/kg bw/day oral rats); unnamed report 2000) NOAELparental: 100 mg/kg bw/day NOAELfertility: 100 mg/kg bw/day (dose range for OECD 443 study) 0,30,100,300 mg/kg bw/day oral rats); unnamed report 2017) study indicated as supporting Ongoing: OECD Guideline 443 (Extended One-Generation Reproductive Toxicity Study)	NOAEL = 10 mg/kg bw-day LOAEL = 60 mg/kg bw-day for effects on cecum (distension, diffuse hyperplasia of mucosal epithelium) Reproductive toxicity: NOAEL = 60 mg/kg bw-day LOAEL = 300 mg/kg bw-day for prolonged oestrous cycle, decreased fertility index, and decreased number of live offspring on PND 4. (ECHA registration 2011)	NOAEL for parental toxicity of 10 mg/kg/d (critical effect: hyperplasia and caecale distension) NOAEL for reprotoxicity of 60 mg/kg/d (critical effects: decrease of the index of fertility, the number of alive births, the number of alive newborn children to PND4, increase of the oestrous cycle). It is however necessary to note that the detail of the study is not available (ANSES 2012)	The dose-range findings study for the OECD 443 study from 2017 in the registration dossier is not included in the evaluation by US EPA (2015) and ECHA (2015) but confirm findings from the OECD 421 study.
Developmental toxicity	NOAELmaternal: 100 mg/kg bw/day NOAELdevelopment: 300 mg/kg bw/day OECD Guideline 414 (Prenatal Developmental Toxicity Study, oral, rats 0,30,100,300 mg/kg bw/day; unnamed report 2014	Not included	Not included	NOAEL= 100 mg/kg bw/day
Endocrine activity	In vitro and in silico Nine studies convering in silico and in vitro data is referenced in the registration dossier. Only overall assessment of these	Based on limited data, it appears that bisphenol S exhibits endocrine activity. In vitro assays demonstrate that bisphenol S can bind to estrogen receptors (ER), elicit estrogen-induced gene transcription, and induce cell proliferation in	BPS possesses oestrogenic properties in vitro. It leads to the proliferation of the mammary cancerous human cells MCF-7 and possesses an affinity for the oestrogens receptors, depending on the model used. BPS is little (even not at all)	

	studies is given., however, no specific details is given). From these it is concluded: "No significant estrogenic activity of 4,4'-sulphonyldiphenol was identified in Yeast test systems. Some estrogenic activity was identified in cell free systems with the estrogen receptor and some estrogenic and antiandogenic activity in mammalian cellular systems (reporter gene assay in MCF7 cells). Though the effect levels observed for 4,4'-sulphonyldiphenol in these test systems were always several orders of magnitude lower in comparison to natural or syntetical agonists" In vivo From data of two uterotrophic assays it was overall concluded: "The very low relative binding affinity observed with 4,4´-sulfonyldiphenol in an in vitro receptor binding assay (logRBA -2.26, Akaori et al. 2008) well correlated to the high dose required to observe a statistically significant effect in the uterotrophic assay (logLED 1.9), as compared to the internal positive control 17beta-estradiol, respectively."	MCF7 cancer cells, and inhibit the androgenic activity of dihydrotestosterone. In an ARE-luciferase reporter assay using a mouse fibroblast cell line, bisphenol S did not elicit an androgenic response, but did inhibit the androgenic activity of dihydrotestosterone. Located data indicate that the in vitro endocrine activity of bisphenol S is approximately 5-7 orders of magnitude less than that of 17β-estradiol, suggesting that bisphenol S acts as a weak estrogen. Comparative in vitro data suggest that the endocrine activity of bisphenol S is somewhat less than that of BPA, bisphenol AP, bisphenol C, and bisphenol F. Limited in vivo data suggest the potential for estrogenic activity. In an uterotrophic assay of rats subcutaneously injected with bisphenol S once daily for 3 days, an apparent estrogenic effect was evidenced by increased absolute and relative uterine weight. Similar effects were elicited by bisphenol F and bisphenol M. Yamasaki, Noda et al., 2004	oestrogenic in the test of yeasts associated with a gene reporter. However, after metabolic activation with S9mix, the oestrogenic activity of BPS increases, what seems to indicate that its metabolites possess oestrogenic properties. In vitro, the oestrogenic activity of the BPS is slightly lower than that of the BPA (of a factor from 2 to 10). An anti-androgenic activity is also observed in a study. An uterotrophic assay on young Sprague-Dawley rats of 20 days (6 animals / doses) was performed according to the OECD guideline 440 (Yamasaki K, 2004). Animals were exposed by subcutaneous injection (vehicle consisted of olive oil) to doses of 0, 20, 100 and 500 mg / kg / day of BPS for 3 days +/- added of 0,6 µg / kg / day of ethinyl estradiol (EE) and sacrificed 24 h after the last administration, and their uterus was weighed. A significant increase of the absolute and relative uterine weight (wet and blotted) in the low and high dose goup but not in the mid dose group. (Yamasaki K, 2004)	
DNEL	0.5 mg/kg bw/day (oral) 1 mg/kg bw/day (dermal)	No reference dose indicated	No DNEL value indicated	

Overview, toxicological profile

Acute toxicity and skin/ eye irritation
Based on the available data low potential for acute oral and dermal toxicity as well as low potential for skin and eye irritation can be concluded.

Skin sensitisation
A recent LLNA study was negative and indicates no concern for skin sensitization. However, it should be noted that three QSAR models rather consistently predict alert for skin sensitization which may warrant some caution (Danish QSAR database, see below). It should be noted that BPA having a rather similar structure as BPS has been identified and is classified as a skin sensitizer.

Repeated dose toxicity
Since the evaluation of US EPA (2015) and ECHA (2015) the REACH registration on BPS has been updated with an OECD 408 (Repeated Dose 90-Day Oral Toxicity in Rats).
In this study BPS was administered by gavage to groups of 10 male and 10 female Wistar rats at dose levels of 0, 100, 300 and 1000 mg/kg bw/d over a period of 3 months. Due to severely impaired body weight development in male animals of the high dose group, i.e. -20% on study day 63, the male animals were treated at a dose level of 600 mg/kg bw/d from study day 70 onwards.

Treatment-related increase in relative liver weights in mid and high dose group in females which correlated with histopathology. In males, the increase in relative liver weights in the high dose group was not accompanied by histopathologic findings but was outside the historical control range (This study: 2.676%, range of historical controls: 2.063% - 2.39%).

Weight increases in the adrenal gland of the high dose group of both sexes and the mid dose females were likely treatment-related although a histopathological correlate was only detected in males of the high dose group.
The increased weights of the ovaries of high dose females were assessed as treatment-related as both absolute and relative weights were outsite with the historical control range (this study absolute / relative 126 mg / 0.061%, historical control range absolute / relative 80.7 - 113.8 mg / 0.036 - 0.051%).

The mammary gland of mid and high dose group males showed a change from the physiological lobulo-alveolar morphology to a tubulo-alveolar appearance with smaller, more basophilic epithelial lining cells.

A dose-dependent increase in incidence and severity of centrilobular hypertrophy was noted as shown in the liver of females. Furthermore, there was an increased incidence of foci of hepatocellular alteration (especially the eosinophilic type) in the high dose females, which was also confirmed by an increased incidence of GSTP positive foci in immunohistochemistry. Focal squamous metaplasia of the uterine glandular epithelium was noted with an increased incidence in treated female animals, which might be treatment-related.

Cecum dilation was macroscopically identified in all high dose males. Histopathological cecum effects were noted in all male and female animals of the high dose group and in one mid dose female animal. Cecum dilation may have had a significant contribution to the decreased bw observed in the high dose males. Though the human relevance of these observations is questionable due to significant anatomical and functional differences of the cecum to rodents in which this structure is large and has a significant function in the digestion.

Increased liver weights in females of the mid and high dose was correlated with a dose-dependent centrilobular hypertrophy was seen in 2/10, 5/10, and 10/10 animals in low, mid and high dose group, respectively. Gradings were minimal in low to moderate in high dose animals correlating with the macroscopic finding “enlarged” in the high dose. In the livers of the high dose females, there was also an increased incidence of mainly eosinophilic foci of hepatocellular alteration, which were confirmed by GSTP immunohistochemistry, and considered to be adverse. Only the hypertrophy in the liver in combination with the increased liver weight of high dose females was assessed as adverse due to the presence of these foci. The hypertrophy alone in low and mid dose groups was assessed as non-adverse as no concurrent findings in clinical pathology were noted.
The increased relative liver weight in high dose males was assessed as adverse together with clinical pathology findings (lower cholesterol and higher triglyceride levels).

In the uterus, focal squamous cell metaplasia of glandular epithelium was observed in 2 females of low and mid dose group and in 5 of 10 females of the high dose group. In the high dose group this finding was assessed as possibly treatment-related and adverse due to the higher incidence. For low and mid dose group animals the finding was assessed as non-adverse as it can occur in single animals in control groups.
The increased weights of the ovaries of test group 3 females were assessed as treatment related although there were no correlating histopathological findings.

Overall, it was concluded by the registrant that BPS related adverse signs of systemic toxicity were observed at a dose level of 300 mg/kg bw/d and above in male animals and at a dose level of 1000 mg/kg bw/d in female Wistar rats. Therefore, under the conditions of the present study the no observed adverse effect level (NOAEL) was 100 mg/kg bw/d in male and 300 mg/kg bw/d in female Wistar rats.

Evaluation:
It may however, be discussed whether also a NOAEL of 100 mg/kg bw/day for female should be concluded, due to significant increased relative liver weight at the two highest dose levels. Therefore, an overall NOAEL of 100 mg/kg bw/day is concluded from the study.

Mutagenicity
BPS has been tested positive for chromosomal aberration without metabolic activation in Chinise hamster ovary cells as well as Chinese hamster lung celles. However, in 2010 BPS was negative *in viv*o in a mammalian erythrocyte micronucleus in mice (OECD Guideline 474, dose levels of 0, 500,1000,2000 mg/kg bw/day). Based on this there is low concern for the mutagenicity of BPS.

Reproduction toxicity
From an OECD Guideline 421 study in rats using dose levels of 0, 10, 60, 300 mg/kg bw/day a NOAELparental of 10 mg/kg bw/day (effects on cecum (distension, diffuse hyperplasia of mucosal epithelium at 30 mg/kg bw/day) and a NOAELfertility of 60 mg/kg bw/day was concluded (prolonged estrous cycle, decreased fertility index, and decreased number of live offspring on PND 4 at 300 mg/lg bw/day).

From an OECD Guideline 422 study in rats using dose levels of 0, 30, 100, 300 mg/kg bw/day a NOAELparental of 100 mg/kg bw/day (effects on cecum (distension, diffuse hyperplasia of mucosal epithelium at 30 mg/kg bw/day) and a NOAELfertility of 100 mg/kg bw/day (prolonged estrous cycle, decreased number of implantations and increased post-implanatyion loss at 300 mg/lg bw/day) was concluded.

Endocrine activity
In vitro assays demonstrate that bisphenol S can bind to estrogen receptors and posses estrogenic acitivy. An uterotrophic assay (OECD guideline 440) has further demonstrated estrogenic acitivity *in vivo* . Thus, it cannot be excluded that the adverse effects on fertility may be a consequence of the endocrine activity.

Additional, recently published data
To supplement these data a literature search was made using the search terms “BPS” or “80-09-1” and/or “metabolism” using Google search and search in the TOXNET database. From this search additional data was retrieved mainly regarding pharmacokinetic properties and on reproduction toxicity.

Metabolism
Song et al. (2017) investigated phase II metabolism of BPS in (ICR) female mice after the oral administration with different dosages (10, 100, 1000 µg/kg body weight. Urinary elimination was the main excretion route for BPS, with the total recovery ranging from 52.8% to 78.1%. In urine, BPS glucuronide (BPS-G) was identified as the predominant metabolite, and the maximum concentrations of BPS-G and BPS sulfate (BPS-S) were obtained at 6 h after the oral administration. BPS was the major compound existed in feces. Only trace amounts of BPS and its metabolites were detected in digestive and excretory related tissues (<1%). Thus, more than 50% of BPS was excreted through phase II metabolism. The authors concluded that due to the biological inactivity of BPS-G and BPS-S, rapid metabolism of BPS to BPS-G and BPS-S may result in reduced toxicity of BPS *in vivo*.

Gys et al. (2018) investigated the in vitro metabolic pathways of BPS using human liver microsomes and cytosol fractions. Liquid chromatography coupled to quadrupole time-of-flight high-resolution mass spectrometry was used for the screening, identification, and structural elucidation of Phase I and II metabolites of BPS. Two Phase I metabolites were formed through hydroxylation of the phenolic rings. Four Phase II metabolites were formed through conjugation with glucuronic acid or

sulfate. Three of these metabolites, namely dihydroxy-BPS, hydroxy-BPS-glucuronide and hydroxy-BPS-sulfate were identified.

Skledar et al. (2016) examined the influence of different metabolic reactions that BPS may undergo on the endocrine activity. Major *in-vitro* phase I biotransformation was determined to be hydroxylation of the aromatic ring of BPS, catalyzed mainly by the cytochrome P450 enzymes CYP3A4 and CYP2C9. However, coupled oxidative-conjugative reactions analyses revealed that glucuronidation and formation of BPS glucuronide is the predominant BPS metabolic pathway. BPS reactive metabolites that can be tracked as glutathione conjugates were not detected in the present study. Two *in-vitro* systems were used to evaluate the endocrine activity of BPS and its two main metabolites, BPS glucuronide and hydroxylated BPS 4-(4-hydroxy-benzenesulfonyl)-benzene-1,2-diol (BPSM1). In addition, two structural analogs of BPS, bis[4-(2-hydroxyetoxy)phenyl]sulfone (BHEPS) and 4,4-sulfonylbis(2-methylphenol) (dBPS) were tested. The test systems were yeast cells, for evaluating estrogenic and androgenic activities, and the GH3.TRE-Luc reporter cell line for measuring thyroid hormone activity. BPS and BPSM1 were weak agonists of the estrogen receptor, EC50 values of 8.4 × 10(-5) M and 6.7 × 10(-4) M, respectively. Additionally, BPSM1 exhibited weak antagonistic activity toward the thyroid hormone receptor, with an IC50 of 4.3 × 10(-5) M. In contrast to BPSM1, BPS glucuronide was inactive in these assays, inhibiting neither the estrogen nor the thyroid hormone receptors. Hence, glucuronidation appears to be the most important pathway for both BPS metabolism and detoxification.

Waidyanatha et al. (2018) investigated clearance and metabolism of BPS and selected bisphenol derivatives in male and female rat, mouse and human hepatocytes. In general, human hepatocytes cleared/ metbolised BPS and other bisphenols (including D-8 and TGSA) derivatives slower than rodents. Of the derivatives examined, the clearance of BPS-MPE, BPS-MAE, 2,4-BPS and TGSA were similar to each other and were the highest and the clearance of D8 and BPS were lower and close to each other. In all species, clearance of 2,4-BPS was higher than BPS. The clearance of D90 was the lowest likely due to the large size of the derivative. There was no apparent sex difference in clearance of BPS and derivatives in rats, mice or humans. In male rats following gavage administration of 50, 150, and 500 mg/kg [14C]BPS the main route of excretion was via urine; the urinary excretion decreased (72 to 48%) and the fecal excretion increased (16 to 30%) with increasing dose. The disposition was similar in female rats and male and female mice following gavage administration. Radioactivity remaining in tissues at 72 h in both species and sexes was ≤2.4%. In bile duct cannulated rats 53% of a gavage dose was secreted in bile suggesting extensive enterohepatic recirculation of [14C]BPS. Following an intravenous dose in rats and mice, the pattern of excretion was similar to gavage. These data suggest that the dose excreted in feces folowing gavage administration is likely the absorbed dose. Urinary metabolites included the glucuronide and sulfate conjugates with a moderate amount of parent. The pattern of *in vitro* hepatic metabolosm was similar to *in vivo* with some difference among derivatives. The data indicated that similar to other bisphenol analogues, BPS was well absorbed following oral expsosure and extensively excreted with minimal tissue retention.

Liver toxicity

Zang et al (2018) investigated liver toxicity in mice orally exposed to 0, 5, 50, 500, or 5000 µg BPS/kg bw/day for 4 or 8 weeks. The highest dose level for 8 weeks resulted in liver injury with increased plasma levels of alanine aminotransferase, aspartate aminotransferase and total bilirubin, as well as defects in hepatic morphology. Moreover, such exposure to BPS induced oxidative stress in the liver of mice by decreasing activities of antioxidant enzymes, and increasing lipid peroxidation level and expression of two biomarker genes, HO-1 and GADD45B. No significant changes were observed for treatment with lower doses (5-500 µg/kg) or shorter duration (4 weeks).

Reproduction toxicity

Ahsan et al. (2018) compared the endocrine disrupting potentials of BPS with BPA, using female rats as an experimental animal model. On postnatal day 1 (PND 1) female pups born were randomly assigned to seven different treatments. Control group received *subcutaneous injection* of castor oil (50 mL). Further, three groups of female pups were *injected subcutaneously* with different concentrations (0.5, 5 and 50 mg/kg in 50 mL castor oil) of BPS, and three groups were treated with 0.5, 5 and 50 mg/kg BPA from postnatal day 1 (PND 1) to PND 10. Highest doses treatments of both compounds resulted in delayed puberty onset and altered estrous cyclicity. Final body weight was significantly high in the highest dose treated groups of both BPS and BPA. Gonadosomatic index, absolute and relative weight of uteri was significantly reduced

in BPS (5 and 50 mg/kg) and BPA (5 and 50 mg/kg) treated groups than control. Plasma concentrations of testosterone and estradiol were significantly increased, while plasma progesterone, Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) concentrations were significantly reduced in highest doses treated groups. Dose dependent increase in the number of cystic follicles in the ovaries was evident along with an increase in the number of atratic follicles. Further the highest doses (50 mg/kg bw/day) resulted in reduced number of pups born The results suggest that neonatal exposure to higher concentrations of BPS can lead to BPA like structural and endocrine alterations in female rats.
Ullah et al (2016) exposed adult male rats in a 30 day oral study to different doses of BPS (0,1, 5, 25 and 50 µg/kg day). Significant increase in the testicular reactive oxygen species and lipid peroxidation were observed in the higher doses tested while antioxidant enzymes activity and protein content were significantly reduced. Plasma and intra-testicular testosterone concentrations were reduced in groups treated with higher doses of BPS. Testicular morphology revealed thin seminiferous epithelium in the treated groups as compared to the control. In the epididymis, area of the tubular epithelium showed significant reduction and empty lumen were observed in the groups treated with higher concentrations of BPS. The present data suggest that BPS has the potential to induce oxidative stress in the testis and might have effect on spermatogenesis in rats.

Tucker et al. (2018) studied whether exposure to bisphenol A, bisphenol AF (BPAF) and bisphenol S (BPS) could affect female pubertal mammary gland development and long-term mammary health in mice. Timed pregnant CD-1 mice were exposed to vehicle, BPA (0.5, 5, 50mg/kg), BPAF (0.05, 0.5, 5mg/kg), or BPS (0.05, 0.5, 5mg/kg) via oral gavage between gestation days 10–17. Mammary glands were collected from resulting femaleoffspring at postnatal day (PND) 20, 28, 35, and 56, and at 3, 8, and 14 months for whole mount, histopathological evaluation,and quantitative real-timepolymerase chain reaction(qPCR); serum steroid concentrations were also measured at these timepoints. In the bisphenol-exposed mice, accelerated mammary gland development was evident during early puberty and persisted into adulthood. By late adulthood, mammary glands from bisphenol-exposed female offspring exhibited adverse morphology in comparison with controls; most prominent were undifferentiated ductends, significantly more lobuloalveolar hyperplasia and perivascular inflammation, and various tumors, including adenocarcinomas. Effects were especially prominent in the BPAF 5mg/kg and BPS 0.5 mg/kg groups. These data demonstrate that prenatal exposure of mice to BPAF or BPS induced precocious development of the mammary gland, and that siblings were significantly more susceptible to spontaneous preneoplastic epithelial lesions and inflammation, with an incidence greater than that observed in vehicle and BPA-exposed animals.

Catanese et al. (2016) investigated the effects of bisphenol S (BPS), on maternal behavior and brain in CD-1 mice orally exposed to 2 or 200 µg/ BPS/kg bw/day during pregnancy and lactation (F0 generation) and in female offspring exposed during gestation and perinatal development (F1 generation). Different effects in F0 and F1 dams for a number of components of maternal behavior, including time on the nest, time spent on nest building, latency to retrieve pups, and latency to retrieve the entire litter were observed. Expression of estrogen receptor α were characterized in the medial preoptic area (MPOA) and quantified tyrosine hydroxylase immunoreactive cells in the ventral tegmental area, 2 brain regions critical for maternal care. BPS-treated females in the F0 generation had a statistically significant increase in estrogen receptor α expression in the caudal subregion of the central MPOA in a dose-dependent manner. In contrast, there were no statistically significant effects of BPS on the MPOA in F1 dams or the ventral tegmental area in either generation. Thus, it was concluded that BPS affects maternal behavior and brain with outcomes depending on generation, dose, and postpartum period.

LaPlante et al. (2017) investigated the effects of bisphenol S (BPS), an estrogen receptor (ER) agonist, on the lactating mammary gland; the arcuate nucleus, a region of the hypothalamus important for neuroendocrine control of lactational behaviors; and nursing behavior in CD-1mice. Female mice were orally exposed to vehicle, 2 or 200 µg BPS /kg/ d from pregnancy day 9 until lactational day (LD) 20, and tissues were collected on LD21. Tissues were also collected from a second group at LD2. BPS exposure significantly reduced the fraction of themammary gland comprised of lobules, the milk-producing units, on LD21, but not LD2. BPS also altered expression of Esr1 and ERa in the mammary gland at LD21, consistent with early involution. In the arcuate nucleus, no changes were observed in expression of signal transducer and activator of transcription 5, a marker of prolactin signaling, or ERa, suggesting that BPS may act directly on the mammary gland. However, observations of nursing behavior collected during the lactational period revealed stage-specific effects on both pup and maternal nursing behaviors; BPS-treated dams spent significantly more time nursing later in the lactational period, and BPS treated pups were less likely to initiate nursing. Pup growth and development were also stunted. The data

indicate that low doses of BPS can alter lactational behaviors and the maternal mammary gland. Together, they support the hypothesis that pregnancy and lactation are sensitive to low-dose xenoestrogen exposures.

Conclusion, BPS

Recent data has shown that BPS is readily absorbed in mice upon oral exposure as urinary elimination alone account for nearly 80% of the given dose. The main metabolites are BPS glucuronide (and BPS sulfate to a lesser extent). Similar metabolites are identified in rodents and humans, however at a slower rate in humans. BPS and the phase I hydroxy metaboilte BPSM1 were weak agonists in an estrogen receptor assay in yeast cells whereas BPS glucuronide was inactive.

The study by Ashan et al. (2018) testing both BPS and BPA on the development of the female reproductive system in rats after subcutaneous injection of similar levels of BPS or PBA from postnatal day 1 to postnatal day 10 show very identical findings in relation to increased body weight gain, delayed puberty onset, altered levels of plasma hormones, increased numbers of cystic follicles and atratic follicles and decreased number of ovulatory follicles. Further the highest dose (50 mg/kg bw/day) resulted in reduced number of pups born. This indicate very similar mode of action of the two substances.

Tucker et. Al (2018) observed effects on mammary gland development in female pups from female mice orally exposed to BPS on gestation day 10-17 at dose levels from 0.5 to 50 mg/kg bw/day. However, no dose-response was found as effects most significantly occurred at the lowest dose level of 0.5 mg/kg bw/day.

Further *in vivo* testing has also been done in specialized study designs at very low oral dose levels of BPS.
LaPlante et al. (2007) found that BPS at very low oral dose levels (2 µg/kg bw/d and 200 µg/kg bw/d) during pregnancy and lactation altered the mammary gland and nursing behavior in mice. At the same dose levels in mice Catanese et al. (2016) noted alterations in maternal behavior towards caring and raising their pups.
Ullah et al. (2016) found changes in testicular morphology and reduced intra-testicular testosterone levels in male rats orally exposed during 30 days at the highest dose levels (dose level range 1 - 50 µg/kg bw/d).
The significance and robustness of the findings from these studies are difficult to interpret and at the moment the data are not considered suitable for serving as starting point for DNEL derivation.

Regarding liver toxicity Zang et al (2018) found histopathological changes in liver of mice exposed 8 weeks at a dose level of 5 mg/kg bw/day of BPS whereas no such findings were noted at the next highest dose level of 0.5 mg/kg bw/day.

Overall, the most critical effects for BPS are considered to be reproductive toxicity regarding fertility effects and repeated dose toxicity regarding effects on cecum (distension, diffuse hyperplasia of mucosal epithelium) and liver. BPS exerts estrogenic activity both in *vitro* and *in vivo*.

DNEL derivation

Option 1

The OECD 421 as reported by ECHA (2015) , US EPA (2015) and the REACH-registration is considered the most critical study for a DNEL derivation study
In the OECD 421 study effects on cecum (distension, diffuse hyperplasia of mucosal epithelium) was observed at a LOAEL of 30 mg/kg bw/day in CD rats (NOAEL = 10 mg/kg bw/day). Similar findings was noted in the OECD 408 study in Wistar rats at a LOAEL of 300 mg/kg bw/day and a NOAEL of 100 mg/kg bw/day.
As a precautious approach the NOAEL of 10 mg/kg bw/day for the most sensitive strain of rats is used as the POD for the DNEL derivation:

DNELoral,consumer = NOAEL / (AFI x AF II x AF III...)

DNEL oral, consumer = 10 mg/kg bw/day / (10 x 10 x 6) = **0.017 mg/kg bw/d**

Where:
AFI is set to 10 (a subfactor of 4 for allometric scaling from rats to humans and a subfactor of 2.5 for remaining differences)
AFII is set to 10 for difference in susceptibility in the general population
AFIII is set to 6 for extrapolation from a subacute study to chronic exposure

Option 2

In the recent study by Zang et al. (2018) a NOAEL and LOAEL regarding liver toxicity in mice was found at 0.5 mg/kg bw/day and 5 mg/kg bw/day, respecitvely in an 8 week oral study.

DNELoral,consumer = NOAEL / (AFI x AF II x AF III...)

DNEL oral, consumer = 5 mg/kg bw/day / (7 x 2.5 x 10 x 4 x 3) = 0.0024 mg/kg bw/d

Where:

AFI is set to 17.5 (a subfactor of 7 for allometric scaling from mice to humans and a subfactor of 2.5 for remaining differences)
AFII is set to 10 for difference in susceptibility in the general population
AFIII is set to 4 for extrapolation from a medium-term study (8 weeks) to chronic exposure
AFIV is set to 3 to extrapolate from a LOAEL to an NOAEL. The NOAEL of 0.5 mg/kg bw/day is not considered an appropriate starting point due to the large spacing between the dose levels in the study.

NB: It should be noted that these DNELs values are lower compared to the DNEL value of 0.5 mg/kg bw/day given by the REACH-registrant that calculated a DNEL value of 0.5 mg/kg bw/day based on the NOAEL of 100 mg/kg bw/day from the OECD 408 study in Wistar rats.

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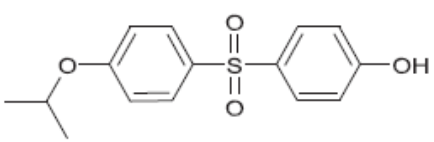
D-8

In the table below data from the expert assessment provided by US EPA (2015) and ECHA (2015) plus the data from the REACH-registration of the substance is gathered for generating an overall toxicological profile of the substance.

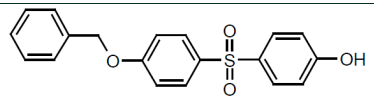
TABLE 14. D-8; CAS 95235-30-6, Classification (REACH registration): No human health classification.

Structure: 	**I** **REACH registration October 2018** **study results (study type; reference)**	**II** **US EPA 2015**	**III** **ECHA 2015**	**Comments/ conclusion**
Absorption, Distribution, Metabolism & Excretion		Estimated to not be absorbed through the skin as neat material and has poor absorption in solution. Can be absorbed through the lung and gastrointestinal tract (Estimated by analogy to BPA)	Refers to data as presented by US EPA (2012)	
Acute toxicity	LD50 > 5 mg/kg bw (no species indicated, no further details on result) (unnamed reports) LC0 inh, rats = 5.04 mg/L (OECD 403, Unnamed report 2003) LD0 dermal, rats = 2000 mg/kg bw (EU method B.3 Unnamed report 1990)	LD50 oral, rats >3200 mg/kg (Eastman Kodak, 1991) LD50 oral, mice >3200 mg/kg (Eastman Kodak, 1991) LD50 dermal, guinea pigs >1000 mg/kg (Eastman Kodak, 1991) LD50 dermal, rats >2000 mg/kg (ECHA 2013) LC50 inh, rats > 5.04 mg/L (ECHA 2013)	No data available	Low concern for acute toxic potential
Skin irritation/corossion	OECD 404 study, rabbits: no conclusion given but all scores for erythema and edema indicated as “0”. (Unnamed report 1986)	No data. Read-across from data on BPS-MPE*: Slight irritant at 24 hours recovering within 2 weeks, guinea pigs (Eastman Kodak, 1991). No skin irritation reported in rabbits, (ECHA, 2013)	Refers to data as presented by US EPA (2012)	Low concern for skin irritation

Eye irritation/ damage	EPA OTS 798.4500 study (acute eye irritation): no conclusion given. Scores indicates no eye irritation potential (Unnamed report 1986)	No data. Read-across from data on BPS-MPE*: Slight irritant, rabbits, clearing within 24 hours (Eastman Kodak, 1991) No eye irritation in rabbits (ECHA, 2013)	Refers to data as presented by US EPA (2012)	Low concern for eye irritation
Skin sensitisation	Negative, OECD Guideline 406 (Skin Sensitisation, GPMT): (key study Unnamed report 1986) Positive, Other non-LLNA in vivo test (not defined): (additional study unnamed report, year?)	No data. Read-across from data on BPS-MPE*: Negative for skin sensitization; 10 guinea pigs (Eastman Kodak, 1991)	Refers to data as presented by US EPA (2012)	Concern for skin sensitization as a skin sensitising potential has been reported from a not further defined study in the REACH registration. Skin sensitising potential further predicted by the Danish QSAR database.
Repeated dose toxicity	NOEL = 50 mg/kg bw/day (OECD 408, 90D oral Wistar rats, Unnamed report 2009, no other details given) NOEL = 10.9 mg/kg-day (males), 11.9 mg/kg-day (females); actual doses received (limited details, (OECD 407, 28D dietary, Fischer 344 rats, no other details given, Unnamed report 1988)	NOAEL = 50 mg/kg-day (highest dose tested) (OECD 408, 90D oral rats, ECHA 2013) NOAEL = 10.9 mg/kg-day (males), 11.9 mg/kg-day (females); actual doses received (limited details, (90D dietary, rats, limited details, ECHA 2013)	Analogy to BPS NOAEL = 40 mg/kg bw/day (oral, rats, 28D) NOAEL = 10 mg/kg bw/day (OECD 421 on BPS)	A NOEL of 50 mg/kg bw/day was identified in an OECD 408 study performed 2009.
Mutagenicity *in vitro*	Negative (±S9), OECD 471, reverse mutation assay in S. typhimurium TA98, TA100, TA1535, TA1537; TA 1538. No further details (unnamed report 1987). Negative (±S9), OECD 473 (In Vitro Mammalian Chromosome	Negative, reverse mutation assay in S. typhimurium TA98, TA100, TA1535, TA1538 (ECHA 2013) Negative, chromosomal aberrations in Chinese hamster lung cells (ECHA 2013)	No data	

	Aberration Test) No further details. Unnmamed report 1988)		
Mutagenicity *in vivo*	Negative, OECD 474 in vivo mammalian somatic cell study: cytogenicity / erythrocyte micronucleus. Unnamed report 2009	Negative, chromosomal aberrations in male/female NMRI mice (ECHA 2013)	No data
Cancer	No data	No data	
Fertility	NOEL(parental) = 125 mg/kg-day NOEL (F1) = 125 mg/kg-day OECD Guideline 415 (One-Generation Reproduction Toxicity Study; Wistar rats, gavage. No details. Unnamed report 2009	Parental toxicity: NOAEL = 10 mg/kg bw-day LOAEL = 60 mg/kg bw-day Reproductive toxicity: NOAEL = 60 mg/kg bw-day LOAEL = 300 mg/kg bw-day (Estimated by analogy to OECD 421 on BPS)	Read-across to data on BPS and conclusion as US EPA (2015)
Developmental toxicity	No data	One-generation oral (gavage) study in rats Parental NOEL = 125 mg/kg-day F1 NOEL = 125 mg/kg-day (ECHA 2013, no study details)	
Endocrine activity	No data	Based on several in vitro studies, there is limited evidence of endocrine activity. D-8 was negative for estrogenicity in two ER binding assays and one competitive ER binding assay, and positive for anti-estrogenicity in a competitive binding assay in the presence of 17β-estradiol.	Refers to data as presented by US EPA (2012)
DNEL	DNEL, consumer = 0.25 mg/kg bw/day (both for oral and dermal exposure)	No reference dose indicated	No DNEL value indicated

*BPS-MPE, structure:



Additional, recently published data
To supplement these data a literature search was made using the search terms “D-8” or “D8” or “95235-30-6” and/or “metabolism” and “toxic” using Google search and search in the TOXNET database. From this search, no further data was retrieved.

Overview, toxicological profile

It has to be noted that only limited toxicological data is available on D-8. Thus, for a proper evaluation of the toxicological profile further data/ details on reproduction toxicity (fertility and development) and repeated dose exposure to D8 is missing.

The key study for sensitization is a GPMT test indicating a negative result, whereas a further study (type not indicated) found a positive response which may indicate a concern for this end-point. Predictions from the Danish DTU QSAR database indicate alert for skin sensitization as two models predict D8 as a skin sensitizer (the Case Ultra model and the SciQSAR model).

The REACH registration derived an oral DNEL for the general population of 0.25 mg/kg bw/day from the NOAEL of 50 mg/kg bw/day in Wistar rats by applying an overall assessment factor of 200.

However, a rather low NOAEL of 10.9 mg/kg bw/day was found in an OECD 407 study (28D) diet study in Fisher rats, indicating a potential for higher degree of toxicity in this rats strain. Due to lack of details for further assessment of the two repeated dose toxicity studies a precautious approach is warranted and thus the NOAEL of 10.9 mg/kg bw/day will be used for calculation of a DNEL value.

DNEL derivation

DNEL = NOAEL / (AFI x AF II x AF III x AFIV x ....)
DNEL = 10.9 mg/kg bw/day / (10 x 10 x 6 x 2) = 0.009 mg/kg bw/d
Where:
AFI is set to 10 (a subfactor of 4 for allometric scaling from rats to humans and a subfactor of 2.5 for remaining differences)
AFII is set to 10 for difference in susceptibility in the general population
AFIII is set to 6 for extrapolation from a subacute 28 day study to chronic exposure
AFIV is set to 2 for low quality of reporting and lack of details and justification.

Conclusion
Non-conclusive equivocal data exists for a skin sensitization potential for D8. Repeated dose toxicity may be a critical end-point as a rather low NOAEL of 10.9 mg/kg bw/day from a 28 days oral study in rats was reported. Based on this an oral DNEL of 0.009 mg/kg bw/day can be estimated.

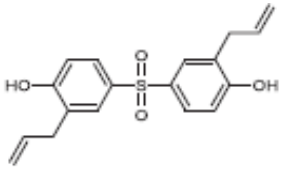
References

ECHA (2015): European Chemicals Agency. Background document to the Opinion on the Annex XV dossier proposing restrictions on 4.4’-isopropylidenediphenol (Bisphenol A; BPA). Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC). 4 December 2015.
US EPA (2015): US EPA. Bisphenol A alternatives in thermal paper. Final report. August 2015. https://www.epa.gov/sites/production/files/2015-08/documents/bpa_final.pdf
Danish QSAR database: http://qsardb.food.dtu.dk/database/index.html search on CAS 95235-30-6

TGSA

In the table below data from the expert assessment provided by US EPA (2015) and ECHA (2015) plus the data from the REACH-registration of the substance is gathered for generating an overall toxicological profile of the substance.

TABLE 15. TGSA; CAS 41481-66-7, classification (REACH registration): Skin Sens 1, H317.

Structure: 	I REACH registration September 2018 Study results (study type; reference)	II US EPA 2015	III ECHA 2015	Comments/ conclusion
Absorption, Distribution, Metabolism & Excretion	No data	Not absorbed through the skin as neat material and has poor absorption in solution. Can be absorbed through the lung and gastrointestinal tract. (Estimated by analogy) Oxidation of the terminal double bonds in the body via an epoxide intermediate is expected. TGSA is a potential cross-linking agent because it has two terminal double bonds. (Estimated by analogy)	Refers to data as presented by US EPA (2012 + 2015)	Low degree of dermal absorption is expected.
Acute tox	Oral LD50 > 2000 mg/kg bw No details Dermal LD50 > 2000 mg/kg bw No details	LD50 oral,rat >2,000 mg/kg (Nippon Kayaku Co., 1991f) LD50 dermal, rat >2,000 mg/kg (Nippon Kayaku Co., 1991d)	Refers to data as presented by US EPA (2012 + 2015)	Low acute toxic potential
Skin irritation/corossion	Non-irritant. Edema and erythema score of “0” for all three tested animals. No further details.	Non-irritant, rabbit (OECD 404; Nippon Kayaku Co., 1991c)	Refers to data as presented by US EPA (2012 + 2015)	Low potential for dermal irritation
Eye irritation/ damage	Non-irritant. Based on scores on iris, cornea, and chemosis.	Minimal irritant, rabbit (OECD 405; Nippon Kayaku Co., 1991e)	Refers to data as presented by US EPA (2012 + 2015)	Low potential for eye irritation
Skin sensitisation	produced a positive result in 14 of 20 animals. No further details negative, epicutaneous test in guinea pigs EU method B6	Weak skin sensitizer in guinea pigs; produced a positive result of 70% (14/20) sensitization rate in guinea pigs in a, GPMT test (OECD 406;	Refers to data as presented by US EPA (2012 + 2015)	Predicted as a skin sensitizer by using CASE Ultra and Leadscope models whereas TGSA is outside applicability domain in the

		Nippon Kayaku Co., 1991h) Non-sensitizer in guinea pigs in Buehler test. (Nippon Kayaku Co., 1992b) Non-sensitizer in local lymph node assay in female CBA/JN mice; applied to dorsum of ears for 3 days; all stimulation indexes were below 3. (OECD 429; Nippon Kayaku Co., 2010)	The classification as Skin Sens. 1 is acknowledged and concern for skin sensitization is concluded	SciQSAR model (Danish QSAR database). The QSAR data support the concern for skin sensitization as critical effect.
Repeated dose toxicity	NOAEL = 15 mg/kg-day LOAEL = 150 mg/kg-day Only data indicated	NOAEL = 15 mg/kg-day LOAEL = 150 mg/kg-day (microscopic renal changes. Increased incidence of basophilic tubules and interstitial mononuclear cell infiltrates in kidneys). (28D oral dosing, rats in OECD 474 mammalian erythrocyte micronucleus test in mice (gavage) at 0,15,150,1000 mg/kg bw/day. Nippon Kayaku Co., 1991j)	Refers to data as presented by US EPA (2012 + 2015) Further it is indicated that STOT RE 2 (kidneys) may be a relevant classification	NOAEL of 15 mg/kg bw/day Kidney considered as target organ
Mutagenicity *in vitro*	No data	Negative ± metabolic activation in S. typhimurium strains TA98, TA100, TA1537, TA1535, and E. coli WP2uvrA (OECD 471; Nippon Kayaku Co., 1991g) Negative for chromosome aberrations in human lymphocytes (OECD 473 Nippon Kayaku Co., 2000c) Negative for sister chromatid exchanges (unnamed ref)	Refers to data as presented by US EPA (2012 + 2015) Low concern for genotoxicity is concluded	

Mutagenicity *in vivo*	No data	Negative, mammalian erythrocyte micronucleus test in mice (gavage). (OECD 474; Nippon Kayaku Co., 1991i)	Refers to data as presented by US EPA (2012 + 2015) Low concern for genotoxicity is concluded.	
Cancer	No data	No data. However, considered of moderate concern due possible formation of side chain epoxide intermediate	Refers to data as presented by US EPA (2012 + 2015)	Inconclusive data lacking
Fertility	No data	No data. Read-across to BPS: Parental toxicity: NOAEL = 10 mg/kg bw-day LOAEL = 60 mg/kg bw-day Reproductive toxicity: NOAEL = 60 mg/kg bw-day LOAEL = 300 mg/kg bw-day (Estimated by analogy) (OECD 421; ECHA 2011)	Refers to data as presented by US EPA (2012 + 2015)	Inconclusive data lacking
Developmental toxicity	No data	No data	No data	Inconclusive data lacking
Endocrine activity	No data	Did not cause significant estrogenic activity in a recombinant yeast screen assay in Saccharomyces cerevisiae; did not bind to estrogen receptor in recombinant yeast; there was an estrogenic response that was 4 orders of magnitude less than 17B-estradiol and 1 order of magnitude less than BPA. (Nippon Kayaku Co., 1999a) Uterotrophic assay in immature rat; No evidence of estrogenic effects on uterus of immature rats at oral doses up to 100 mg/kg bw. (Nippon Kayaku Co., 1999b)	Refers to data as presented by US EPA (2012 + 2015)	No evidence of estrogenic effects in the uterotrophic assay in vivo
General comments	Very insufficient reporting	Primary source of information	Refer to US EPA assessment	

DNEL	No DNEL value indicated	No reference dose indicated	No DNEL value indicated	DNEL = 0.025 mg/kg bw/day (oral, consumers), se below

Additional, recently published data
To supplement these data a literature search was made using the search terms “TGSA” or “41481-66-7” and/or “metabolism” and “toxic” using Google search and search in the TOXNET database. From this search, no further relevant data was retrieved.

Overview, toxicological profile

It has to be noted that only limited toxicological data is available on TGSA and these data relate to US EPA (2015). Thus, for a proper evaluation of the toxicological profile data on reproduction toxicity (fertility and development) and sub-chronic exposure to TGSA is missing.

As indicated in the table above the critical effects of TGSA can be identified to be skin sensitization and organ toxicity from repeated short-term exposure.
No threshold level for skin sensitization can be identified but at DNEL value for systemic effects can be calculated for consumers in relation to oral exposure based on the data on repeated short-term toxicity.

From a 28D oral rat study a NOAEL of 15 mg/kg bw/day has been identified based on kidney toxicity observed at higher dose levels of 150 mg/kg bw/day and 1000 mg/kg bw/day. Based on this a consumer DNEL for repeated exposure can be calculated according to the methodology described in ECHA guidance R8 (2015).

DNEL derivation
DNEL oral,consumer = NOAEL / (AFI x AF II x AF III)
DNEL oral, consumer = 15 mg/kg bw/day / (10 x 10 x 6) = 0.025 mg/kg bw/d

Where:
AFI is set to 10 (a subfactor of 4 for allometric scaling from rats to humans and a subfactor of 2.5 for remaining differences)
AFII is set to 10 for difference in susceptibility in the general population
AFIII is set to 6 for extrapolation from a subacute study to chronic exposure

Conclusion, TGSA
Skin sensitization can be concluded as critical effect of TGSA by dermal exposure. No safe threshold can be indicated.
An oral long-term DNEL for consumers of 0.025 mg/kg bw/d can be estimated to protect against kidney toxicity

References
ECHA (2015): European Chemicals Agency. Background document to the Opinion on the Annex XV dossier proposing restrictions on 4.4’-isopropylidenediphenol (Bisphenol A; BPA). Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC). 4 December 2015.

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Survey and risk assessment of developers in thermal paper

In December 2016, the European Commission decided to restrict the usage of the developer bisphenol A (BPA) in thermal paper to max. 0.02 weight percentage; a restriction that comes into force in January 2020. The aim of this survey is, thus, to assess the development of developer usage and to collect information on which alternative developers are in use in thermal paper on the Danish market, the contents and migration of developers from selected applications of thermal paper as well as risk assessment of developers in these applications.

Screening analysis have been made of six developers; BPA, BPS, BPS-MAE, TGSA, Pergafast and D-8. After that, migration analyses for the primary developer i six selected samples. The health-related risk of TGSA, D-8 and BPS by migration was calculated in each of their own scenarios.

The report point out, that the data used for the assessments is limited, and that there are uncertainties in both exposure estimates and DNEL calculations, which does not provide a foundation for representative risk assessment conclusions on the usage of thermal paper.

The increased knowledge about the harmful effects of BPS strengthens the assumption of BPS having harmful effects similar to those of BPA. The use of alternatives with allergenic properties may be considered worrying in products with skin contact, since the migration risk must be considered problematic.

This report indicates that increased and more systematic knowledge of the harmful effects of the alternative substances and their migration from point-of-sales receipts is needed to obtain a basis for more accurate risk assessments.

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