10 Bisphenol A: contested science, divergent safety evaluations

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Bisphenol A (BPA) is currently one of the world's best-selling chemicals and primarily used to make polycarbonate plastics. It is widely used in common products such as baby bottles, household electronics, medical devices and coatings on food containers. BPA is known to mimic the female hormone oestrogen and has been found to leach from the materials where it is used.

Studies have suggested that even exposure to low doses of BPA may cause endocrine disrupting effects. As with other hormones, it appears that an organism is most sensitive during development but that effects are often not observed until much later in the lifecycle. This means that at the time when the effects become detectable, the chemical exposure has vanished. This makes it extremely difficult to link exposure to effects in humans.

This chapter maps some of the findings in studies of rodents and humans. It also discusses the challenges of evaluating scientific findings in a field where industry-sponsored studies and independent scientific research seem to deviate strongly. The authors offer suggestions for ways to uncouple financial interests from scientific research and testing.

A widely used and dispersed industrial chemical like Bisphenol A is a controversial example of an endocrine disrupting substance that has implications for policymakers. Different approaches to risk assessment for BPA by US and European authorities are presented. It throws light on the ways in which similar evidence is evaluated differently in different risk assessments and presents challenges for applying the precautionary principle.

The intense discussion and scientific work on BPA have slowly contributed to a process of improving test strategies. While traditional toxicology has relied on a monotonic increasing dose-response relationship as evidence that the effect is caused by the test agent, studies on BPA and other endocrine disruptor chemicals (EDCs) have demonstrated the limitations of this approach and adjustments have been made in some cases.

It has also been widely accepted that effects cannot be predicted by simply thinking of BPA as a weak oestrogen and extrapolating from what is observed for more potent endogenous oestrogens. This lesson is particularly evident in the intense pharmaceutical interest in selective oestrogen response modifiers (SERMs).

The chapter is followed by a panel analysing the value of animal testing for identifying carcinogens.

([1]) This paper is based on the scientific opinions of the authors and does not necessarily reflect the opinions or policies of the institutions they are working for.

10.1 The first known endocrine disruptor: early warnings

Bisphenol A (BPA) is one of the industrial chemicals often referred to as 'emerging environmental substances'. This categorisation is in fact somewhat euphemistic. BPA was probably the first synthetic substance known to mimic the natural female sex hormone oestrogen. As early as 1934, Dodds and Lawson (1936, 1938) were searching for synthetic chemicals that could replace expensive natural oestrogen in pharmacological applications. They identified BPA as a weak functional oestrogen, utilising rat test systems that are still in use today. It failed to make a career as a medicine. Later, other substances like Diethylstilbestrol (DES) were discovered by the same team of British scientists (Dodds et al., 1938). The synthetic oestrogen DES was much more potent than BPA and was subsequently used as a pharmaceutical that showed severe side effects (Meyers, 1983).

Not suitable as a pharmaceutical, BPA was marketed as an industrial chemical. In 1957 BPA was polymerised with phosgene, resulting in what is known today as polycarbonate. That started the plastics revolution that has changed the lives of people around the world. At that time everyone thought that plastics, particularly polycarbonate, were significant advances that would improve our lives.

10.2 A growing problem

BPA is currently one of the world's best selling chemicals, with a total annual production of 3.8 million tonnes in 2006 (Association of Plastics Manufacturers, Polycarbonate/BPA group, 2007). In 2005 and 2006, about 1.15 million tonnes were consumed within the European Union (European Commission, 2008). These figures reflect an increase in consumption of 69 % over a seven year period, an annual increase of 7 to 8 %. Most BPA is used to produce plastics, mainly polycarbonate (66 %) and epoxy resins (33 %) (Association of Plastics Manufacturers, Polycarbonate/BPA group 2007). Many other uses have been identified, such as an ingredient in thermal paper. This is why BPA is regularly found in recycled paper (Terasaki et al., 2007; Vinggaard et al. 2000), which is frequently used to produce food containers (Ozaki et al., 2006; Lopez-Espinoza et al., 2007).

It should be noted that the European Risk Assessment Document was not able to identify the purpose of use of more than 7 000 tonnes of the BPA that is consumed annually within the European Union (European Commission, 2008). Commercial BPA contains up to 16 different phenolic impurities that show structural features of oestrogenic chemicals but have never been toxicologically characterised. These 'minor impurities' represent another 10 000 tonnes annually (Terasaki et al., 2004).

Leaching from plastics

Two out of three tonnes of BPA produced are used to manufacture polycarbonates. This clear hard plastic material is increasingly used where transparent and low-weight synthetic materials are wanted; DVDs, modern car roofs and headlight covers, baby bottles and plastic dishes for use in microwave ovens are all made of polycarbonate. These plastic materials can easily be identified by the recycling code 07 in a triangle or the letters PC. Though BPA is a covalently-bound building block of polycarbonates, the monomer is subsequently released over time from the plastic material (Krishnan et al., 1993; Tan and Mustafa, 2003). Leaching of BPA is increased by the age of the material, alkaline conditions and heating. All polycarbonate items are probably a source of BPA. This gives rise to the concern that a growing stock of material has been built up in our homes and in the environment that is a potential continuous source of BPA exposure.

Polycarbonates are probably the main but not the only source of BPA. It also leaches from dental sealants (Joskow et al., 2006), inner coatings of cans and microwave containers (Brotons et al.,1994; Mariscal-Arcas et al., 2009), and in relatively high concentration from medical devices used in intensive care units (Calafat et al., 2009). Thus BPA is found in many matrices including house dust (Butte et al., 2001), indoor air, hand wipes, solid food, liquid food (Wilson et al., 2007) and drinking water (Shao et al., 2008). The European Union Directive 90/128/EEC includes BPA in the list of chemicals with a specific migration limit in food, set at 3 mg/kg (European Commission, 1990). BPA has been found in canned food at concentrations up to 380 μg/kg (Goodson et al., 2002), but only up to 4.5 μg/kg in canned drinks (Cao et al., 2009).

It is not surprising that BPA is one of those ubiquitous chemicals that are a real nightmare for analytical chemists. The substance can leach easily from plastic laboratory equipment and thus contaminate samples that are to be analysed. As with softeners such as phthalates, great care has to be taken to avoid such contamination.

10.3 Identifying the risk was an accident, not the result of a regulatory process

In 1991, a conference taking place in Wingspread Racine, Wisconsin used the phrase 'endocrine disruptor' for the first time (Markey et al., 2002). In 1992 the first scientific paper using this was published by Bason and Colborn (1992). It described indicators of hormonal de-regulation in wildlife and humans and suspected mainly pesticides as the cause of these emerging effects. BPA was added to the list of potential endocrine disruptors one year later. It was by accident that the risks associated with it were re-discovered. In 1993 a team of endocrinologists at Stanford University found an unknown oestrogenic substance that contaminated their assays. Finally they identified BPA leaching from their polycarbonate cell culture dishes when they were autoclaved (Krishnan et al., 1993). It may be surprising that neither any governmental nor any industry programme for risk identification or risk assessment identified BPA as a problematic hormonally-active substance although such programmes had been run in Europe since 1982 with considerable financial and intellectual input from governments and industry. Although several European chemical companies had a history of hormone research over decades, they did not play a role in identifying and assessing environmental chemicals with hormone-disrupting properties. Industry missed a chance to care for their products responsibly.

In 1995 a number of workshops took place in Denmark, the United Kingdom, Germany and the United States to discuss the upcoming issue of hormonally-active environmental chemicals. One year later the book by Colborn, Dumanowski and Myers (1996) 'Our stolen future', with a foreword by former US Vice-President Al Gore, put this issue on the global political agenda. Meanwhile, in the second half of the 1990s, BPA became the most prominent example of an endocrine disruptor in the scientific and public debate.

10.4 Bisphenol beyond Paracelsus

In the past 100 years almost no toxicological textbook failed to quote Philippus Aureolus Theophrastus Bombast von Hohenheim, better known by his nickname Paracelsus:

> 'Alle Ding sind Gift und nichts ist ohn Gift; alein die Dosis macht das ein Ding kein Gift ist' (Paracelsus, 1539)
>
> (All things are poison and nothing is without poison, only the dose permits something not to be poisonous).

Probably all students of toxicology were taught by their professors that sugar and salt and even water can be a poison if the dose is high enough. BPA challenged our belief that high doses produce more serious effects than low ones. Instead, BPA, like natural hormones, frequently produces dose-response curves that are non-linear. In such experiments very low doses or concentrations show a small effect, intermediate doses cause the most serious effects while high concentrations again show no or only moderate effects. These dose-response curves resemble an upside-down 'U' and are therefore called inverted u-shaped dose-response curves (Sonnenschein et al., 1989). Such dose-response curves occur when tumours are induced in transgenic mice (Jenkins et al., 2011), in snail test systems with regard to clutch size (Schulte-Oehlmann et al., 2001), serum estradiol levels in rats (Akingbemi et al., 2004), calcium influx in rat pituitary cells (Watson et al., 2007), effects on pupal weight and sex ratio in the housefly (Izumi et al., 2008), and reproductive performance in female mice (Cabaton et al., 2011) when these animals are exposed to BPA (Figure 10.1).

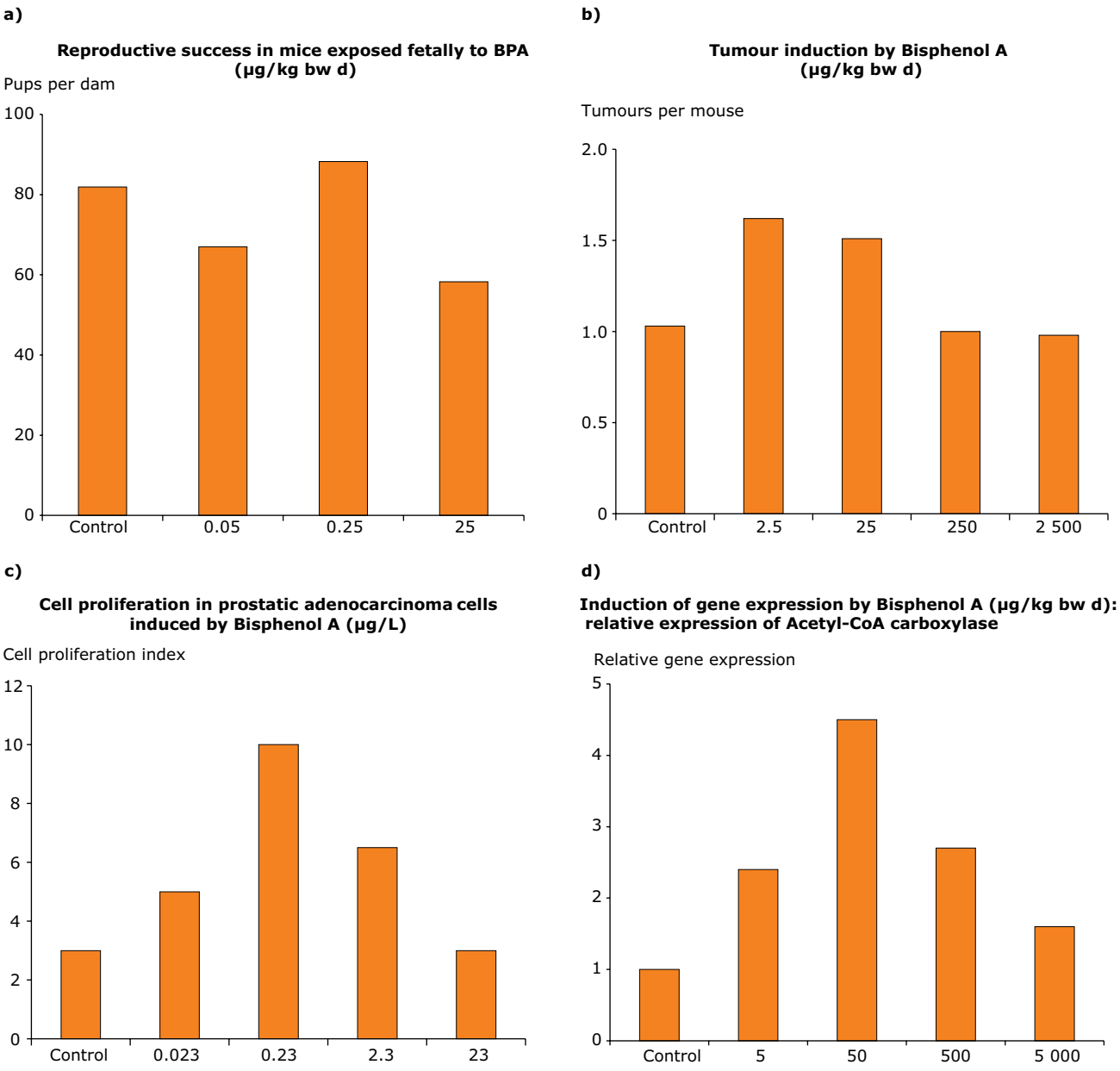
Several mechanisms have been hypothesised to try to explain this phenomenon. The global assessment of state-of-the-science of endocrine disruptors published on behalf of the International Programme for Chemical Safety (IPCS) of the WHO (Damstra et al., 2002) pointed out that no common dose-response mechanism can be expected when endocrine disruptors are under study. These chemicals often mimic naturally-occurring hormones or antagonise them. So they interfere with a naturally-activated system that may be stimulated by low doses and inhibited by over-dosing because receptor-mediated responses saturate (Welshons et al., 2003). Several different mechanisms involving activation of different genes may be involved in the expression of one visible effect. An endocrine-disrupting mechanism resulting in a u-shaped dose response curve may be the result of two or more effects with different dose-response characteristics each, as demonstrated in experiments using cell line models. These non-monotonic effects have been shown experimentally in many *in vivo* and *in vitro* systems (Vandenberg et al, 2012). Although the Endocrine Society, the largest professional organisation of endocrinologists, points out in a recent statement that non-traditional dose-response relations are very common in the action of hormones (Diamanti-Kandarakis et al., 2009), the existence and plausibility

of such effects are still disputed by some scientists and members of regulatory bodies (Sharpe, 2010).

Deviations from monotonic dose-response curves for hormone action are very frequent. Neither do they seem to be rare in toxicology. In 2001, Calabrese and Baldwin analysed 668 dose-response curves that were published in toxicological or eco-toxicological papers in three major journals from 1962–1998: 37 % of the curves were non-monotonic and exhibited a u-shaped form.

This kind of curve is much more than a curiosity. What toxicology did in past centuries was to extrapolate from high doses with frequent and serious effects to low doses where only small effects were expected. A prerequisite for doing this is that the curve is monotonic. The central paradigm of

Figure 10.1 Examples of non-monotonic dose-response curves for BPA



Note: In the test systems shown, small doses show small effects, intermediate doses cause the most pronounced effects while high doses cause no change or even a decrease in effect.

Schematic graphs adopted from the papers, for data and details see the original references.

Source: a) Data from Cabaton et al., 2010; b) Data from Jenkins et al., 2011; c) Data from Wetherill et al., 2002; d) Data from Marmugi et al., 2011

toxicological assessment was: if a high dose of a chemical does not cause harm, then a low dose will not either. Obviously this does not hold true at least for physiological responses to endocrine disruptors. After 500 years it has become clear that Paracelsus's paradigms do not contribute to the protection of human health and environment if they are applied to risk assessments in a naive way.

1997 Colerangle and Roy reported that a low dose of BPA induced a proliferative effect in breast tissue and that BPA was much more potent than expected from its oestrogen-receptor binding profile. Science reacted immediately and since then hundreds of papers on low-dose effects have been published (see Table 10.1). These further demonstrate that the organism is most sensitive during development, that effects are often not observed until later in the lifecycle, and that conventional toxicology testing could be insensitive to BPA if it fails to include in-utero dosing and later life follow-up of appropriate endpoints. The papers also support the observation of non-monotonic dose-response curves for BPA and other hormones, reflecting feedback mechanisms, receptor saturation, and multiple mechanisms of action (Vandenberg et al., 2012). Within the scientific community, there is far-reaching agreement on these concepts and findings. However BPA industry organisations continue to claim that these findings are invalid as 'no study purporting to show low-dose effects has been replicated in a second lab, despite repeated efforts to do so' (Polycarbonate/BPA Global Group, 2012).

10.5 The time makes the poison

The proper development of an organism is an extremely complex process, dependent on external and internal cues and hormonal regulation. Not only the chemical characteristic and the internal dose are important but also the exact timing of the stimulus (Neubert, 1997). For BPA, so far, it has been shown that irreversible developmental effects are caused during the foetal, neonatal or juvenile period in test animals (Palanza et al., 2008) and that the effects observed may be different if the organism is exposed during early or later life-stages (Richter et al., 2007).

Assessing the effects of endocrine disruptors is extraordinary difficult because the time of exposure is not necessarily the time when the effects can be detected. Perinatal exposure to BPA has been shown to affect females: it alters ovarian cyclicity and induces early cessation of oestrus cycles, impairs reproduction, interferes with sexual differentiation of the brain, alters behaviour, alters mammary gland development and induces mammary gland neoplasia (Soto and Sonnenschein, 2010). It has also been shown that BPA can interfere with normal spermatogenesis, reducing sperm numbers later in life in rodents and when the mothers of the pups are dosed during pregnancy and lactation (vom Saal et al., 1998; Okada et al., 2008a). If this also happens in humans, the effects of exposure of the foetus or the newborn may only be seen more than a decade later when the boys reach puberty and sperm becomes available for characterisation. This temporal disconnection between exposure and effect is even larger when the effect observed is breast cancer, because the age of prevalence for this disease is 50–60. For example, prenatal exposure to synthetic oestrogens like DES (Hoover et al., 2011) increase the incidence of breast cancer at 40 years of age or older. At the time when the effects become detectable the chemical exposure has vanished. This makes it extremely difficult to apply epidemiological methods to link exposure to effects in humans. For a realistic risk assessment it is also crucial to characterise the exposure to BPA at the appropriate life stage. Young children have the highest rate of daily ingestion of this chemical (European Commission, 2008) and the internal concentrations of free and toxicologically-active BPA may be much higher than in adults because of their different metabolic capacity (Edginton and Ritter, 2009).

These examples illustrate that dose is only one of the factors that make a poison. Equally important are the time of exposure and the time when effects become visible. For a long time BPA has been erroneously viewed as only a weak oestrogen (Völkel et al., 2005; Goodman et al., 2009). Indeed, *in vitro* studies indicated that BPA competes with estradiol to bind the oestrogen receptors alpha and beta. In these tests relative binding affinities were at least a thousand-fold lower than that of estradiol (Kuiper et al., 1998). Recent results from *in vivo* and *in vitro* studies indicate that BPA can act via a number of different additional cellular target systems, including binding to a non-classical membrane-bound oestrogen receptor (ncmER) (Nadal et al., 2000, 2004; Alonso-Magdalena et al., 2005), an orphan nuclear receptor called oestrogen-related receptor gamma ERR-γ (Okada et al.. 2008b), a seven-transmembrane oestrogen receptor called GPR30 (Thomas and Dong, 2006), and the aryl hydrocarbon receptor (AhR) (Kruger et al., 2008).

In vitro studies also show that BPA can act as an androgen receptor antagonist. BPA can also interact with thyroid hormone receptors (TRs) (Moriyama et al., 2002; Zoeller et al., 2005). These multiple modes of action have recently been reviewed in a number of papers (NTP, 2008; Chapin et al., 2008; Wetherill et al.,

2007). In some of these systems BPA can exhibit equal or even stronger potency than the naturally occurring hormones (Wozniak et al., 2005; Watson et al., 2007).

For a long time influential scientists claimed that low-dose findings were neither credible nor plausible because, from the relative binding strength of oestrogen and bisphenol, considerably lower effects of BPA would have been expected (Greim, 2004). Today we know that their expectations were based on inappropriate assumptions. Recent experiments showing that low-dose effects of BPA are abolished in null mutants of nuclear oestrogen receptors provide irrefutable evidence in this regard (Soriano et al., 2012).

Nowadays there is widespread agreement that BPA is an endocrine-active chemical with multiple modes of action. A recent paper from US Environmental Protection Agency (EPA)'s high throughput testing group, ToxCast, showed that BPA was active in a wide variety of mechanistic assays — one of the most active chemicals tested (Judson et al., 2010) — and a literature review from a US National Toxicology Program (NTP) draft report on obesity provides an excellent review of BPA's multiple modes of action (NIEHS/NTP, 2011).

10.6 Concern or no concern: that is the question

When BPA was polymerised to make polycarbonate, neither the data on non-monotonic dose responses nor the deleterious effects of foetal exposure to DES were known or commonly recognised in science. In addition, since BPA seemed to be a weak oestrogen with activity 1 000–10 000 fold less than estradiol, and since it was assumed that the BPA monomer would not be released from the polycarbonate plastic (Biles et al., 1997), there was no real concern about human exposure and thus toxicity.

The complexity of the exposure assessment, the toxicological profile of BPA, and probably the high economic importance of this substance may have contributed to the fact that risk assessments for this substance differ more markedly than for any other chemical. A number of scientific and regulatory bodies and committees have published risk assessments for BPA. The identified acceptable doses for humans differ by many orders of magnitude.

10.7 BPA reviews and risk assessments

BPA is regulated as a food contaminant and thus falls under the jurisdiction of the Food and Drug Administration (FDA) in the US and the European Food Safety Authority (EFSA) in the EU. Both agencies have provided risk assessments over the past decade, all based on toxicity tests in experimental animals. These regulatory agencies have essentially used Good Laboratory Practice (GLP) guideline studies as the only source of data on the toxicity of BPA (see Box 10.1 for GLP and Good Scientific Practice).

Let's take a look at the GLP guideline studies that have been done to assess BPA toxicity and

Box 10.1 Good Science and Good Laboratory Practice

Science is a self-regulating system. To ensure high quality standards, scientists have developed rules for themselves on how to perform scientific work. These have been laid down by international organisations like WHO (2006) or national scientific societies like DFG (1998) in Germany in comprehensive guidance documents. A peer-review system is the core instrument for safeguarding these rules. As a prerequisite for publication, results and scientific papers are reviewed by peer scientists. In prestigious journals more than three out of four papers are not accepted for publication. This system is a very rigorous form of quality control.

For regulatory purposes, particularly for the testing of chemicals and pharmaceuticals, not all results and procedures need to be published and peer-reviewed. As a reaction to low quality and fraud, a different system of quality control has been established. The system of Good Laboratory Practice (GLP) (OECD, 1998) has been tailor-made for commercial research laboratories, and regulatory agencies worldwide require that this system is applied for tests conducted to fulfil regulatory requirements. GLP regulates how to conduct protocols and report tests. GLP can give technical advice but cannot judge whether a test is appropriate to solve a problem or whether, for example, the relevant outcomes have been studied. GLP does not indicate that good science has been performed or that the scientific results are adequate and sufficient to protect human health and the environment (for comprehensive discussion, see also Myers et al., 2009).

that have been pivotal in the FDA and EFSA risk assessment. There are two multigenerational reproduction studies in rats (Tyl et al., 2002) and one multigenerational mouse study (Tyl et al., 2008) that were regulatory guideline studies done according to GLP. These studies all showed only non-specific toxicity (number of live pups per litter) and they were used to identify a Lowest Observed Adverse Effect Level (LOAEL) of 50 mg/kg body weight per day (bw d) and a No Observed Adverse Effect Level (NOAEL) of 5 mg/kg bw d. At least in the rat study there were significant effects below this level (Heinze and Chahoud, 2003). These effects were regarded as not relevant by the authors. The studies have been criticised because they use traditional toxicological endpoints that cannot detect subtle developmental changes and effects caused by hormones (Myers et al., 2009). Recently a large independent trans-generational study (Ryan et al., 2010) also could not find effects at low doses on behaviour, puberty and fertility of female rats.

On the other hand there are many *in vivo* studies describing developmental effects in rodents at very low doses (Table 10.1). The effects under study were reproductive organ morphology, neurodevelopment and behaviour, male reproductive health, and immunology. At least 46 peer-reviewed published studies report effects at oral doses of 50 μg/kg bw d or less (see Table 10.1) (for review, see Gies, 2007). This dose has been regarded as a safe Acceptable Daily Intake (ADI) in the recent European assessment of the European Food Safety Agency (EFSA, 2010).

Recently a working group of the French health agency ANSES (2011) carefully re-examined all animal studies with low doses of BPA, assessed their quality and compared their results. The panel concluded that animal experiments show effects that could be confirmed on male sperm production, induction of ovarian cysts, endometriosis, and advanced puberty in females. Behavioural effects have been confirmed for maternal behaviour and sexual dimorphic behaviour such as anxiety. Effects on lipogenesis, immune behaviour and breast development were also regarded as confirmed.

An important aspect of dose-response assessment is that it is still not clear what is a no-effect level for BPA's most sensitive end-points. Further research is needed to continue refining methods to reliably assess sensitive endpoints and to conduct the studies with a sophisticated approach to connecting internal free BPA dose with effects. As these studies are pursued, we may find that effects of BPA occur in the low or sub- pg/ml range, the same range as estimates of current human exposure. It is clear that most sensitive endpoints include effects on mammary gland development (Rudel et al., 2011b) and neuro-behavioural endpoints that are not commonly assessed in toxicity studies, even those recently adopted for testing endocrine-active chemicals.

The different assessment documents weight this evidence differently. The main areas of controversy are:

- Do any of the non-GLP peer-reviewed papers that show effects of BPA at low doses contain sufficiently reliable information to be considered in the risk assessment? Putting this question the other way: is the study sponsored by The Society of the Plastics Industry, Inc. (Tyl et al., 2002) and the study of Ryan et al. (2010) so reliable that nearly all other studies can be dismissed?

- Are there any relevant concentrations of free BPA in the body that can cause biological effects or is this substance so readily metabolised that it cannot harm humans?

The assessment of the European Food Safety Agency (EFSA) 2010 and the Risk assessment report of the European Union (European Commission, 2008) state that none of the low dose studies has the quality to provide data for the risk assessment. All these studies have been dismissed. The reasons given were:

- only one or two doses tested;

- low number of animals;

- inadequate statistical processing of the data;

- results not consistent with other studies.

The application of these criteria was used to exclude or ignore significant peer-reviewed scientific results. The fact that they were peerreviewed and published in reputable scientific journals indicates that the members of the scientific community that reviewed all these many papers do not agree with the criteria chosen by EFSA.

10.8 EFSA and EU risk assessments

EFSA identified the study of Tyl et al. (2002) as pivotal. With an assessment factor of 100 applied to the No Observed Adverse Effect Level (NOAEL) an Acceptable Daily Intake (ADI) of 50 μg/kg bw d

was derived. It should be noted that the assessment of the EFSA and other regulatory bodies is based on arbitrarily selected data from this study. The original data from this study showing a significant increase in anogenital distance (AGD) in males but not in females were not taken forward to the risk assessment (Heinze and Chahoud, 2003). Although AGD is not a validated endpoint for regulatory studies, it is an important marker of sexual development in rodents and humans. Changes in AGD show that sexual development has been disturbed (Swan et al., 2005; Longnecker et al., 2007). An increase in AGD is considered a surrogate for virilisation, while a decrease indicates de-masculinisation. In humans, a lower AGD has been shown to be a predictor of poor semen quality in later life (Mendiola et al., 2011). Similar changes of AGD due to low doses of BPA have been found in independent studies in rodents by Gupta (2000) and Somm (2009). In a recent paper, Tyl (2009) the principal author stated that no low-dose effects have been found in this study. This is not in line with the data presented.

EU Risk Assessment Report (RAR)

In contrast to the majority of EU Member States, some Nordic Countries regarded four neuro-behavioural studies as valid for risk assessment (Negishi et al., 2004; Carr et al., 2003; Ryan and Vandenberg, 2006; Adriani et al., 2005). In a footnote to the assessment document they proposed to take these as pivotal studies. The lowest effective concentration in these studies was described by Adriani as 40 μg/kg bw d. With a factor of three for extrapolation from LOAEL to NOAEL and an extrapolation factor of 100 this would result in an ADI of 0.13 μg/kg bw d. This ADI would be lower by a factor of 380 than that of EU RAR.

The National Toxicology Program (NTP) of the United States of America (NTP, 2008). The NTP assessment concluded that BPA was clearly toxic at high doses over 5 mg/kg bw d. In contrast to the EU RAR, NTP does include the results of the low-dose studies in their assessments. Although it states that low-dose effects are difficult to interpret in many cases, NTP concludes that these results should not be dismissed. The low-dose studies provide limited evidence that human health may be affected and there is some evidence that human health may be at risk at current exposure levels. NTP does not indicate a 'pivotal' study but in their risk characterisation they base their estimates on developmental effects reported from mice studies at a dose of 2.4 μg/kg bw d.

NTP did not calculate a Tolerable Daily Intake (TDI) in its assessment. If one applies routine methods to derive an Acceptable Daily Intake (ADI), with a factor of 3 for extrapolation from LOAEL to NOAEL and an extrapolation factor of 100, this would result in an ADI of 0.008 μg/kg bw d. This ADI would be a factor of 6 250 lower than that derived by the EFSA.

Environment Canada and Health Canada (2008). The 2008 Canadian assessment states that 'collectively these (low dose) studies provide evidence that exposure to BPA during gestation and early postnatal life may be affecting neural development and some aspects of behaviour in rodents, the overall weight of evidence was considered limited from the perspective of rigour'. Nevertheless, taking a precautionary approach, the Canadian authorities decided to characterise BPA as a substance that may constitute a risk to humans. So the precautionary risk assessment is based on low-dose neuro-developmental studies. It is not stated which of the studies are taken as decisive. In 2010 the Canadian government listed BPA as a toxic substance.

The Chapel Hill Consensus statement (vom Saal et al., 2007) is not a risk assessment in the classical sense. Thirty-eight scientists, including most of the leading scientists working on BPA, expressed confidence that low doses of BPA disrupt development in many animal models. Their key message is that action is warranted when internal exposure of humans reaches or exceeds the levels that cause serious effects in experimental animals in low dose studies. This consensus statement clearly points to the developing gap between scientific knowledge about BPA and the published opinions of regulatory committees.

The US Food and Drug Administration (FDA, 2008, 2010). In 2008 the FDA issued its risk assessment of BPA which stated that the 'no observable adverse effect' level of 5mg/kg bw d was an adequate margin of safety. The scientific committee of the FDA established a subcommittee in 2008 to review this assessment. The subcommittee harshly criticised the FDA assessment. In particular, it did not agree that the large number of non-GLP studies should be excluded from the safety assessment.

It stated that the weight of the evidence provided scientific support for use of a point of departure substantially (i.e. at least one order of magnitude) lower than the 5 mg/kg bw d level selected in the draft FDA assessment.

In summary the Subcommittee concluded: 'Coupling together the available qualitative and quantitative information (including application of uncertainty factors) provides a sufficient scientific basis to conclude that the Margins of Safety defined by FDA as 'adequate' are, in fact, inadequate.' The Scientific committee of the FDA later adopted this opinion of its subcommittee. Such an explicit statement fundamentally criticising the work of an agency by its scientific advisors is unprecedented.

The report of its scientific advisory committee resulted in the FDA changing its position. On 10 January 2010, the FDA stated that they now 'have some concern about the potential effects of BPA on the brain, behaviour and prostate gland in foetuses, infants and younger children' (FDA, 2010). Thus, for the first time, while it did not change its actual risk assessment of the acceptable daily intake level, it did acknowledge the existence and possible importance of investigator-initiated studies. At that time there were more than 800 investigator-initiated studies published on BPA toxicity.

European Food Safety Authority 2010 BPA Risk Assessment (EFSA, 2010). In 2010 EFSA released an updated risk assessment of BPA. They basically reiterated what they stated in 2006, that BPA was safe to human health and noted that there had been no new compelling non-GLP studies published on BPA. At that time there were more than 800 investigator-initiated studies that were not included in the BPA risk assessment, each one discarded for not meeting specific guidelines.

Thus at that time, the FDA and EFSA still relied exclusively on a handful of GLP multi-generational studies done in contract laboratories that assessed only reproduction, body and organ weights, clinical chemistry and organ histopathology using H&E staining. The same endpoints had been used for the past 50 years: before endocrine disruptors were known, before the developmental basis of disease and gene expression and epigenetics were known, and before low-dose and non-monotonic dose responses were known.

It is remarkable that the FDA and EFSA used guideline studies to indicate that BPA is safe while ignoring over 800 peer-reviewed studies that showed toxicity of BPA at exposure levels below the level of human exposure.

Certainly there are data gaps, but the practice of regulatory agencies of disregarding, or worse, declaring unfit every peer-reviewed study that does not follow the guideline study design cannot be defensible. The scientific literature needs to be assessed on the basis of the strength of the individual studies and the overall strength of the evidence of all the studies in order to show the same or similar effects across doses and times and species.

The German Federal Environment Agency (UBA) (2010). The view of the German Federal Environment Agency (UBA) is that there are sufficient grounds for concern. Numerous studies present, on the whole, a consistent picture, so that, despite uncertainties and gaps in knowledge concerning risk assessment and levels of exposure, there is need for action. The UBA is therefore in favour of precautionary action and restrictions on the use of certain products that contain BPA.

The French Agency for Food, Environmental and Occupational Health and Safety, ANSES (2011). Based on an analysis of all the available scientific literature, an ANSES scientific expert group found 'that there were proven effects in animals (effects on reproduction, effects on the mammary gland, effects on metabolism, the brain and behaviour) and other suspected effects in humans (effects on reproduction, the metabolism of sugars and fats, and cardiovascular diseases). These effects were demonstrated at doses that were significantly lower than the reference doses used for regulatory purposes, especially during certain periods of life characterised by susceptibility to the effects of BPA (pregnancy, pre- and post-natal periods)' (ANSES 2011). This assessment questions parts of EFSA's current assessments.

A joint ANSES and EFSA paper has recently been prepared (EFSA and ANSES 2011). This paper shows that differing assessments persist, partly because they evaluated evidence at different stages of the risk assessment and partly because they use different study quality criteria ([2]).

10.9 Bisphenol A in human bodies

There is little controversy about the external exposure of humans to BPA. The EU Risk Assessment Report

([2]) ANSES and EFSA agree that they have covered different stages of the risk assessment process: ANSES a hazard identification and EFSA a hazard characterisation (2010) and a full risk assessment (2006) from dietary exposure to BPA (2006). This represents one of the reasons for the divergences between their respective work in 2011 and 2010. They recognise that their selection of critical effects is not based on the same study evaluation criteria e.g. routes of exposure (EFSA and ANSES, 2011).

(European Commission, 2008) used two exposure models to estimate human daily intake. One of these was for regional exposure and one for local exposure near a BPA production plant. Total human exposure was calculated by the regional model to be 1.49 µg/kg bw d, and by the local model to be 43 µg/kg bw d. Estimates of daily BPA intake in adults fell within the range 0.008–1.5 µg/kg bw d. Worst-case scenarios for young children estimated up to 11–13 µg/kg bw d. These data, calculated from exposure scenarios, are well in accordance with daily intake figures recalculated from concentrations in urine. Daily intakes estimated from the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (CDC NHANES) bio-monitoring data range from 0.15–0.22 µg/kg bw d for adults aged 20–60+ years at the 95th percentile (this means that 95 % of the people had concentrations at or below this value) (LaKind and Naiman, 2011). In German children aged 3 to 14, the 95th percentile of the daily intake recalculated from urine concentrations was 0.37 µg/kg bw d and the maximum value among 599 children was 7 µg/kg bw d (Becker et al., 2009). These intakes were similar to those found in children aged 6 to 11 in the US (Calafat et al., 2008). Bottle-fed infants have two times higher urine BPA levels than breast-fed infants (Völkel et al., 2011). Children in neonatal intensive care units have median urinary BPA concentrations about ten times higher than in children aged 6–11 (Calafat et al., 2008; 2009) and 20 participants eating food with limited packaging for three days showed a 66 % reduction in urinary BPA (Rudel et al., 2011a). In studies that report both conjugated and free BPA in urine, > 90 % is conjugated, including in neonates (Calafat et al., 2009). This indicates that there are particularly highly exposed risk groups in vulnerable life phases that have not yet been recognised in current risk assessments. A recent analysis of NHANES data showed that BPA levels did not decline rapidly with fasting time as expected. This suggests significant levels of exposure not related to food, or accumulation in body tissues. The recent finding of transdermal exposure points to additional sources of exposure, and thus to a higher than expected total BPA exposure (Stahlhut et al., 2009)

Major differences exist concerning internal exposure. Only free bisphenol is believed to be biologically active while its conjugated metabolites are probably inactive; however, it should be considered that conjugated metabolites that may be found in the blood can be de-conjugated in peripheral tissues and thus become re-activated. Human bio-monitoring studies from Germany and the US (Schönfelder et al., 2002a; Padnmanabhan et al., 2008) found 4–6 ng/ml free bisphenol in the blood of mothers. These results are almost identical although the studies used totally different techniques. However pharmacokinetic studies (Doerge et al. 2011a), together with data from bio-monitoring studies and model calculations, resulted in estimates of free BPA levels in human blood between 0.1 and 10 pg/ml (Fisher et al., 2011), around three orders of magnitude lower than the above-mentioned directly measured ones.

No free BPA above the detection limit of 2 ng/ml was found in the blood of nine volunteers dosed intentionally with 5 mg/person (Völkel et al., 2002). This study is still the basis of the risk assessment of the EFSA suggesting that no relevant internal concentrations of free BPA can be found in humans. In summary, the EU Risk Assessment report states: 'Considering the evidence as a whole, EFSA concluded that the validity of the reported high blood levels of BPA in unintentionally exposed human subjects is questionable.' Again EFSA ignores consistent results from peer-reviewed scientific work.

New pharmacokinetic studies (Prins et al., 2011; Doerge et al., 2010, 2011; Taylor et al., 2011) show that caveats in this field are legion. Of particular relevance, the Taylor et al study shows that BPA pharmacokinetics is similar in primates and rodents and thus that rodents are suitable models. Moreover routes of exposure, such as dermal exposure (Stahlhut et al., 2009; Liao and Kannan, 2011a, b) and excretion, such as sweat (Genuis et al., 2012), have recently been recognised but have not yet been quantified and thus are additional sources of uncertainty.

Risk assessment is only a protocol used by the regulatory community, not science per se. Uncertainty has to be taken into account and has to be quantified. The plethora of peer-reviewed research showing low-dose effects indicates that applied test protocols and regulatory procedures are not suitable for assessing endocrine disruptors.

A recent review extensively discusses the relevance of measurements of free and conjugated BPA in human blood (Ginsberg and Rice, 2009). Many peripheral organs, including the placenta, show high activity of glucuronidases and sulphatases that are able to cleave conjugated BPA to its free and metabolic active form. Finding the conjugated form in the blood does not predict that the substance is biologically inactive in the tissue. The assumption of EFSA that rapid conjugation protects humans from adverse effects is far from being precautionary.

In contrast the National Toxicology Program (NTP) recognises the possibility that the published values of free BPA may, in some cases, not accurately represent the 'true' concentrations of free BPA in the blood or body fluids of humans or laboratory animals. However, because of the similarity between values reported with different analytical methods, the NTP accepts the published values as sufficiently reliable for use in this evaluation.

10.10 Spheres of influence

In the case of BPA, a large body of scientific literature obviously indicates deleterious effects in rodents at low doses. The effective doses in these studies overlap the doses of current human intake. Most of the European, American and Asian authorities declare BPA to be safe. Industries rely on these risk assessments. Massive pressure from consumers and politicians has forced many companies, for example the major American baby bottle manufacturers and a European aluminium drinking bottle manufacturer, to withdraw their BPA-releasing products from the market. Without doubt, this has had considerable negative effects on the image of the companies, the reputation of their brands and on the earnings of these branches. For many people the question arises whether BPA-producing industries had previously influenced the assessment processes. Such industrial influences on scientists and authorities have been well documented for the risk assessment of tobacco smoke and second-hand smoking in particular (Grüning et al., 2006).

At least one consulting company that had been active for the tobacco industry, the Weinberg Group, has been successfully hired by the BPA industry to influence the European assessment, in particular the classification and labelling (C&L) which is a key instrument for the risk management of chemicals. In its internet presentation the Weinberg Group itself proudly admits:

'In Europe, THE WEINBERG GROUP and its associates have had a five-year long history of working on the polycarbonates/BPA issue… It also includes identification of opponent's likely arguments, and formation of responses to counter these arguments. THE WEINBERG GROUP contributed its academic and regulatory network to the advocacy effort. This approach proved very effective, as ultimately the C&L working group did not follow the recommendation of the Rapporteur Member State to classify BPA as a Category 2 reproductive toxicant, agreeing instead on the more benign Category 3 classification .We have a long-term relationship with this client, and will continue to support this industry as it faces persistent NGO attacks on its products' (The Weinberg Group, 2005).

Classification as a category 2 reproductive toxicant would have required labelling this substance with a skull and bones sign as toxic. Moreover under the new chemical legislation of the European Community, every use of BPA would have required a formal authorisation.

Science is vulnerable. It is based on the independence of scientists and of science itself. In the committee of the European Food Agency AFC — (Panel on additives, flavourings, processing aids and materials in contact with food) nine of the 21 members stated, in the conflict of interest statements they supplied to the agency, that they had worked for at least one company or association under the influence of the industry or for industry itself or had strong links with associations like Greenfacts or ILSI Europe that are dependent on financial support or industries including BPA producers. One member received financial benefits from industry for writing a review (Dekant and Völkel, 2008) on BPA for a scientific journal.

Meanwhile the European Food Safety Authority made considerable efforts to strengthen transparency and scientific independence, as 'the value of its scientific advice is directly linked to the level of trust held in it by the public and therefore seeks to guarantee independence in all aspects of its governance and scientific activities (EFSA, 2012). New rules for independence policy have been launched by EFSA recently.

Without doubt, working for the chemical industry and its organisations or other NGOs is a job like any other. Whether it is wise to give people who are directly or indirectly paid by industry the task of controlling industry may be questioned.

Various scientific papers have investigated whether the outcomes of scientific studies are dependent of the source of funding. In most cases, a significant association has been found (Lesser et al., 2007; Moses et al., 2005; Blumenthal, 2003). An association of funding and outcome can also been detected for studies on BPA (Table 10.2).

Since EFSA reassessed BPA in Europe in 2006 and increased the tolerable daily intake by a factor of five, scientific evidence has accumulated that

shows low dose toxicity and doubts have occurred whether EFSA's decision was unbiased:

- At least ten additional peer-reviewed papers were published showing effects in rodent offspring at oral doses lower than the Tolerable Daily Intake set by the EFSA (see Table 10.1). BPA has been shown to influence body weight and metabolism (Somm, 2009; Rubin et al., 2001) and may be one of the factors contributing to the increasing rates of obesity in humans.

- Numerous other *in vivo* and *in vitro* studies indicate that BPA may not be safe at doses we are currently exposed to.

- Bio-monitoring studies showed that some European and American children are exposed to doses that can produce adverse effects in rodents (for review, see Betts, 2010).

- Vulnerable and highly exposed subgroups, like children in intensive care units, that are not sufficiently covered by current exposure assessments, have been identified (Calafat et al., 2009).

- New sources of BPA have been identified like pacifiers and warm-water tubes (Shelby, 2008).

- Epidemiological studies show that higher exposure of mothers to BPA is associated with increased aggressiveness of daughters when they are two years old (Braun et al., 2009). Like other cross-sectional studies, these associations are not a proof of causation but should be regarded as additional warning signs.

- Free BPA concentrations are associated with oocyte quality (Fujimoto et al., 2011) and embryo quality indicators (Bloom et al., 2011) during human *in vitro* fertilisation.

- BPA levels in the blood of workers are negatively associated with male sexual function (Li et al., 2010).

- Higher BPA exposure is associated with obesity in the general population in the US (Carwile et al., 2011).

- BPA exposure in workers is negatively correlated with the birth weight of their offspring (Miao et al., 2011).

- Gestational BPA exposure affected behavioural and emotional regulation at three years of age, especially among girls (Braun et al., 2011).

- EFSA's assumption that internal doses of free BPA are lower in humans than in rodents at comparable doses is unproven (Gies et al., 2009).

- The European Union has banned baby bottles containing BPA. This ban became effective in 2011 (EU, 2011).

10.11 Lessons to be learned

The 'late lesson' with respect to BPA is the 'same old story' of putting a chemical into widespread use without understanding its health implications, and then trying to resolve public health questions while facing the intense pressure of serious economic consequences. The competing urgency of public health and economic stakes puts the scientific process under enormous pressure. In this perspective the story of BPA resembles those of asbestos, polychlorinated Biphenyls (PCB) and Diethylstilboestrol (DES).

Best science and transparency

In Europe it is timely to dare to start again with the risk assessment of BPA. This assessment must be transparent and conducted by the scientists authoring the papers with high scientific impact in this field. Stakeholder conferences may serve as a forum to make the interests and influence of industry and other NGOs transparent.

Precaution

Until final decisions are made, precautionary measures should be taken to lower human exposures to well below those that cause adverse effects in rodents and behavioural changes in humans in epidemiological studies. This would mean terminating those uses of BPA involving close contact with humans via food or the environment.

Towards more independent science

The new European chemicals legislation REACH (**R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emical substances) relies on the activities of the industry for most risk assessments and toxicity test data. The case of BPA clearly

Table 10.1 Summary of mammalian studies on BPA with effect levels at or below 50 µ/kg bw d, oral administration

Dose (µg/kg bw d)	Organism, age at dosing	Effect	Reference
0.2	Rat, 2-generation study	Anogenital distance in F 1 males, 2 µg/kg in F1 females and 20 µg/kg in F2 females	Ema et al., 2001
0.2	Rat, male adult	Superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase activity in liver ↓, H_2O_2, lipid peroxides ↑	Bindhumol et al., 2003
0.2	Rat, male adult	Prostate size ↑, Testis, epididymis size ↓ H2O2, lipid peroxides ↑	Chitra et al., 2003
0.6	Mouse, pregnancy	Effects on mammary gland development	Ayyanan et al., 2011
1	Rat, 3-generation study	Paired ovary weight in F2 generation ↓, uterine weight in F0 ↓, anogenital distance in female F2 ↓ (Effects were not regarded as relevant by the authors)	Tyl et al., 2002
1.2	Rat, 3-generation study	Litter size ↓, sperm number and motility ↓, post implantation loss ↑	Salian et al., 2009
2	Mouse, pregnancy	Testis and epididymal weights ↑ in offspring	Ashby et al., 1999
2	Mouse, gestation day 11–17, offspring	Aggression ↑, testis weight ↓ in offspring	Kawai et al., 2003
2	Mouse, gestation day 11–17, offspring	Prostate weight ↑, epididymis weight ↓	vom Saal et al., 1998
2	Gerbil, females, 3 weeks after pairing	Changed maternal behaviour	Razzoli et al., 2005
2	Mouse, prenatally, early postnatally	Anxious behaviour ↑ in offspring	Ryan et al., 2006
2	Rat, 3-generation study	Spermatogenesis, sperm quality	Peknicova et al., 2002
2.4	Mouse, gestation day 11–17	Vaginal opening, first oestrus in offspring	Howdeshell et al., 1999
2.4	Rat, male, Postnatal day 21–35	LH, Testosterone and oestrogen levels ↓	Akingbemi et al., 2004
2.5	Mouse, 5 wk	Immune, IFN-gamma and IgG2a ↓	Sawai et al., 2003
2.5	Mouse, pregnancy and lactation	Brain, kidney liver and testes weight ↓, oxidative stress markers ↑ in offspring	Kabuto et al., 2004
2.5	Transgenic mice	Tumour development ↑	Jenkins et al., 2011
5	Mouse, adult male	Testis and seminal vesicle weights ↓	Al-Hiyasat et al., 2002
10	Mouse, gestation day 14–18	Maternal behaviour in offspring	Palanza et al., 2002
10	Mouse, gestation day 14–18	Number and size of dorsolateral prostate ducts in offspring ↑	Timms et al., 2005
10	Mouse, gestation day 11–18	Long-term alteration in neurobehavioral functions in females	Laviola et al., 2005
10	Mouse, gestation day 11–day 8 post partum	Decreased sex differences in behaviour	Gioiosa et al., 2007
10	Rat	Increased prostate hyperplasia	Wu et al., 2011
10	Rat, neonatal	Increased oestrogen-induced prostate intraepithelial neoplasia	Prins et al., 2011
15	Rat, last week of pregnancy	Male behaviour in 6-9 week old offspring altered	Fujimoto et al., 2006
20	Mouse	Chromosomal aberrations, aneuploidy ↑	Hunt et al., 2003
20	Rat, 13 wk	Spermatogenesis ↓	Sakaue et al., 2001
20	Rat, pregnancy	Vaginal morphology in offspring	Schönfelder et al., 2002b
25	Mouse, gestation day 8–23	Structural and histological changes of prostate in offspring	Ramos et al., 2001
25	Mouse, female adult	Number of embryo resorptions ↑, uterine weights ↑	Al-Hiyasat et al., 2004
25	Rat, lactating	DMBA induced carcinogenicity in breast tissue of offspring	Jenkins et al., 2009
25	Mouse, pregnancy	DMBA induced carcinogenicity in breast tissue of offspring	Weber Lozada and Keri, 2011
30	Rats during pregnancy and lactation	Less pronounced sexual behaviour in male offspring, reversed sex differences in brain development	Kubo et al., 2003

Table 10.1 Summary of mammalian studies on BPA with effect levels at or below 50 µ/kg bw d, oral administration (cont)

Dose (µg/kg bw d)	Organism, age at dosing	Effect	Reference
30	Mouse	Immune responses ↑	Yoshino et al., 2003
40	Rat, gestation day 14–postnatal day 6	Sex associated behavioural changes in offspring ↑	Dessí-Fulgheri et al., 2002
40	Rat, pregnancy and lactation	Aggression behaviour in offspring	Farabollini et al., 2002
40	Rat, pregnancy and lactation	Pain sensitivity (hyperalgesia) in offspring	Aloisi et al., 2002
40	Rat, pregnancy and lactation	Changes in spontaneous and amphetamine induced behaviour in offspring	Adriani et al., 2003
40	Rat, pregnancy and lactation	Decrease of playful interactions in offspring	Porrini et al., 2005
40	Rat, pregnancy and lactation	Changes in maternal behaviour in adult females	Della Seta et al., 2005
40	Rat, male PND 23–30	Brain estrogen receptor number altered, testosterone ↓	Ceccarelli et al., 2007
40	Rat, pregnancy and lactation	Spatial recognition memory impaired in offspring, changes in female exploration behaviour	Poimenova et al., 2010
40	Rat, pregnancy and lactation	Impairment of memory, sexual behaviour and locomotor activity in offspring	Goncalves et al., 2010
40	Mouse, day 32–87	Elimination of sex differences in non-reproductive behaviour	Xu et al., 2011
45	Mouse, gestation and weaning	Memory impairment associated with reduction of acetylcholine production in the hippocampus in the male offspring	Miyagawa et al., 2007
45	Mouse, gestation and weaning	↑ Morphine-induced hyperlocomotion and rewarding effect in offspring	Narita et al., 2006
50	Mouse, gestation day 16–18	Anogenital distance and prostate size ↑, epididymal weight ↓ in offspring	Gupta, 2000
50	Rat, gestation and lactation	Deficits in male sexual behaviour in adulthood	Jones et al., 2010
50	Rat, gestation and lactation	Body weight ↑, impaired glucose tolerance, serum insulin ↓	Wei et al., 2011

Note: This table is not comprehensive. Many other studies with other application routes show similar effects. These studies should also not be dismissed for risk assessment purposes as it has been shown that other routes of exposure result in similar internal exposures in the animals.

Source: Taylor et al., 2008, modified from Gies, 2007.

Table 10.2 Outcome of studies on BPA and source of funding

Source of funding	Harm	No harm
Government	94 (90.4)	10 (9.6)
Chemical corporations	0 (0)	11 (100)

Note: Number of studies and percentage in brackets.

Source: Data from Hughes and vom Saal 2005, including studies published until 2004.

shows that the results of industry-sponsored studies and independent scientific studies deviate strongly. Independent science and regulatory toxicology seem to speak different languages. Numerous papers from different laboratories indicate risks at low doses, BPA industry-sponsored studies need doses orders of magnitude higher to produce any effects and if effects are detected they are not taken forward to the risk assessment.

Independent science is interested in finding the effects of a substance and publishing these findings. Independent laboratories usually specialise in a biological system and often have decades of experience in this field. Contracting laboratories have to cover a broad range of endpoints with different chemicals. Thus academic laboratories may be better qualified for testing for subtle changes such as those in early development and behaviour. Also, contract laboratories are per se not economically independent from the producers of a chemical. This has to be considered when weighing the evidence produced by academic research and by contract laboratories.

Independence of scientific advisors to regulatory agencies has been a controversial issue within the scientific community. These problems are obviously not restricted to the case of BPA. A number of measures have been proposed to strengthen scientific independence within the risk assessment process (Holland et al., 2012).

Uncoupling of financial interests and scientific and regulatory research and testing seems to be necessary. Chemical regulation should be based on science and the basis of science is independence. This independence of researchers can be achieved if laboratories are not contracted directly by industry. Research laboratories could be paid by a fund that is financed by the industry, over which industry has no control and which is managed by governments.

The case of BPA shows that results of independent science are of great value and should have an adequate weight within the decision-making process. Without doubt, standard testing by contract laboratories has its value in risk assessment procedures and regulations but their results must not outweigh those from independent academic laboratories. However, there is a need to update the standard testing procedures to incorporate the new knowledge acquired through independent research.

Strengthening the independence of scientific advisors is necessary and timely. Close cooperation with industry or industry-dominated bodies like the International Life Science Institute (ILSI) may be regarded as incompatible with the degree of independence required for advisory bodies.

Transparent and reliable documentation of possible conflicts of interest has not yet been achieved in all cases.

Performing or reviewing risk assessments for public agencies is time-consuming. Experts have to be paid adequately for doing this work. This would allow attracting the best qualified and independent scientists. Both testing and assessment can be financed by charging industry a fee. The employers of these qualified members of the scientific community (universities, research institutions) should be required by government agencies to decrease the workload of these scientists so that they can perform this important service to society.

10.12 Lessons learned

The intense discussion and scientific work on BPA have slowly contributed to a process of improving test strategies. While traditional toxicology has relied on a monotonic increasing dose-response relationship as evidence that the effect is caused by the test agent, studies on BPA and other endocrine disruptor chemicals (EDCs) have demonstrated the limitations of this approach and adjustments have been made in some cases. For example, the US NTP Expert Panel report on BPA (NTP-CERHR, 2007) and the report of the French ANSES 2011 included both single dose and multiple dose studies in their compilations of studies that are useful for evaluating the risks of BPA (Arnich et al., 2011). It has also been widely accepted that effects cannot be predicted by simply thinking of BPA as a weak oestrogen and extrapolating from what is observed for more potent endogenous oestrogens, and this lesson is widely evident in the intense pharmaceutical interest in selective oestrogen response modifiers (SERMs), although some investigators persist in referring to BPA simply as a weak oestrogen.

Under its testing guideline programmme, OECD is currently modifying its guidelines and incorporating many new endpoints that are sensitive to hormonal perturbation, such as timing of vaginal opening, and anogenital distance.

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