BISPHENOL A: INFORMATION SHEET

LOW-DOSE HYPOTHESIS UNPROVEN FOR BISPHENOL A

Summary

Bisphenol A (BPA) is an important industrial chemical that is used primarily to make polycarbonate plastic and epoxy resins, both of which are used in a wide variety of applications. The potential toxicity of BPA has been examined extensively with numerous safety studies conducted over more than 40 years. These studies uniformly have shown that the toxicity of BPA is low, as assessed by standard test protocols. Exposure evaluations have demonstrated a large margin of safety between any realistic exposure levels of BPA and any level of concern. Taken together, these tests and evaluations demonstrate that consumer exposure to BPA does not pose any risk to human health.

In recent years, a hypothesis has been advanced claiming that exposure to extremely low doses of certain substances could cause adverse health effects in humans. According to this "low-dose hypothesis", health effects occur at doses far below levels previously determined to be safe using well-established toxicological procedures and principles. This hypothesis further asserts that health effects may only be observed at low doses while much higher doses result in no effects, which is contrary to a fundamental principle of toxicology – "the dose makes the poison."

Since the initial claims of low-dose health effects of BPA were first reported in the mid-1990s, many studies have been conducted to test the validity of the low-dose hypothesis. Included are definitive large-scale multi-generation studies as well as studies aimed at replicating the results of studies reporting low-dose effects. No low-dose effects were found in these studies, thus clearly demonstrating that the low-dose hypothesis is not valid.

The weight of scientific evidence clearly supports the safety of BPA and provides strong reassurance that there is no basis for human health concerns from exposure to low doses of BPA.

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Introduction

Bisphenol A (BPA) is an important industrial chemical that is used primarily to make polycarbonate plastic and epoxy resins, both of which are used in a wide variety of applications. For example, polycarbonate is used in eyeglass lenses, medical equipment, water bottles, digital media (e.g. CDs and DVDs), cell phones, consumer electronics, computers and other business equipment, electrical equipment, household appliances, safety shields, construction glazing, sports safety equipment, and automobiles. Among

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the many uses for epoxy resins are industrial floorings, adhesives, industrial protective coatings, powder coatings, automotive primers, can coatings and printed circuit boards.

The potential toxicity of BPA has been examined extensively with numerous safety studies conducted over more than 40 years. These studies uniformly have shown that the toxicity of BPA is low, as assessed by standard test protocols. Exposure evaluations have demonstrated a large margin of safety between the exposure levels of BPA and any level of concern. Taken together, these tests and evaluations demonstrate that consumer exposure to BPA does not pose any risk to human health.

In recent years, a hypothesis has been advanced claiming that exposure to extremely low doses of certain substances could cause adverse health effects in humans, including disruption of normal hormonal functions. In science, a hypothesis is a limited statement regarding cause and effect that has not been confirmed through repeated experimental tests. According to this "low-dose hypothesis", health effects occur at doses far below levels previously determined to be safe using well-established toxicological procedures and principles. The hypothesis further asserts that the dose-response relationship for these substances is "non-monotonic", which means that health effects may only be observed at low doses while much higher doses result in no effects. The claimed non-monotonic dose-response relationship of the low-dose hypothesis is contrary to a fundamental principle of toxicology – "the dose makes the poison."

The low-dose hypothesis is largely based on several small-scale experimental studies that report reproductive or developmental effects in mice or rats from low doses of BPA. Several attempts to confirm the hypothesis by repeating these initial experiments have shown that the results cannot be replicated, which indicates that the hypothesis is not valid. More importantly, definitive large-scale experiments using accepted protocols have also found no evidence for reproductive or developmental effects from low doses of BPA. Consequently, a number of independent scientific bodies, after reviewing all available evidence, have concluded that the low-dose hypothesis is unproven. The following sections provide a brief summary of key experimental findings and the conclusions of the scientific bodies that have comprehensively reviewed the scientific evidence.

BPA Low-Dose Effects Not Confirmed

The low-dose hypothesis for BPA originated with several small-scale studies first reported in the 1990's. These studies triggered concerns over possible health effects from low-dose exposure to BPA and, as a result, data from the initial studies has been re-evaluated and additional studies have been conducted to determine if the low-dose hypothesis is valid. In addition to showing that the low-dose hypothesis is not valid, the additional re-evaluations and research have also highlighted shortcomings of the initial studies that may account for the reported low-dose effects. Several of the key studies are described in this section.

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Definitive Large-Scale Studies

The most definitive tests of the validity of the low-dose hypothesis for BPA are two large-scale reproductive and developmental toxicity studies using accepted protocols. Both of these studies clearly demonstrated the absence of a low-dose effect of BPA.

The most comprehensive of these is a three-generation study conducted at the Research Triangle Institute (now RTI International) under the direction of Dr. Rochelle Tyl (Tyl *et al*, 2002). In this study, Sprague-Dawley rats (30 males and 30 females per dose group) were fed a diet containing BPA at levels from 0 to 7500 parts per million, yielding approximate intakes of 0, 0.001, 0.02, 0.3, 5, 50 or 500 mg/kg body weight/day. Exposures were continued until adulthood of the third-generation offspring. The endpoints evaluated included parental growth rate, food intake, reproductive performance, sperm production and motility, gross and histopathology, organ weights, litter size, pup survival and growth, and anogenital distance. In addition, the day of vaginal opening, preputial separation and (in males) the presence or absence of retained nipples were recorded. Analysis of the data for all of these endpoints for the parental and three offspring generations revealed no evidence of a low-dose effect of BPA. This exceptionally powerful study, which complied with Good Laboratory Practice (GLP) standards, clearly demonstrated the absence of low-dose effects for BPA.

The Tyl study was thoroughly re-evaluated as part of an independent, scientific peer review of the evidence for and against "low-dose endocrine disruptor" effects organized by the U.S. National Toxicology Program (NTP Report, 2001). The peer review included a Statistics Subpanel that re-evaluated the experimental design, data analysis and interpretation of results of studies claiming low-dose effects as well as studies that found no evidence of low-dose effects. In recognition of its significance, the NTP Statistics Subpanel stated that the Tyl study is "arguably the most comprehensive of the studies we evaluated."

In a similar study commissioned by the Japanese National Institute of Health Sciences and carried out by the Chemical Compound Safety Research Institute (Ema *et al*, 2001), Crj:CD (SD) IGS rats were dosed orally by stomach tube over two generations. The doses applied were 0, 0.2, 2.0, 20 or 200 µg/kg body weight/day of BPA. Endpoints assessed included parental growth, food intake, reproductive performance, sperm production and motility, gross and histopathology, organ weights, litter size, pup survival and growth, and anogenital distance. In addition, the study measured reflex development, maze performance, and several hormones related to reproduction. Analysis of the data for all of these endpoints for the parental and two offspring generations revealed no evidence of a low-dose effect of BPA, which is fully consistent with the results of the Tyl study. The Ema study was also re-evaluated by the NTP peer review panel and the results were fully confirmed (NTP Report, 2001).

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Small-Scale Studies

In contrast to these two definitive studies, reports of low-dose effects for BPA have generally been based on small-scale experiments that included a small number of doses (i.e. sometimes as few as one or two), tested many fewer animals per dose group (i.e. as low as five to seven), did not comply with GLP standards, and frequently used a route of exposure that is not relevant to humans (i.e. subcutaneous or intraperitoneal injection). When other scientists tried to repeat the small-scale studies on a larger scale with more animals and doses, the results of the small-scale studies could not be reproduced. In some cases, even the re-evaluation of the original data from the initial study has revealed that the reported effects cannot be substantiated.

For example, researchers from the University of Missouri (Nagel *et al*, 1997) reported an increase in prostate weight in male offspring of CF1 mice that were exposed to BPA during pregnancy at 2 or 20 µg/kg body weight/day. This study included only 7 females per treatment group and 11 unexposed controls, and only one male from each litter was examined. In a subsequent publication (vom Saal *et al*, 1998) derived from the same study, the authors reported that the 2 µg/kg body weight/day dose decreased body weight and epididymis weight. Preputial gland weight was reported to be increased although seminal vesicle and testis weights were unaffected. The 20 µg/kg body weight/day dose was associated with a 20% reduction in daily sperm production per gram of testis weight, but that dose had no statistically significant effect on body, preputial, epididymal, seminal vesicle or testis weight. These parameters were apparently all assessed in the same individual males per litter as were used in the first report (Nagel *et al*, 1997), but only 5 males per BPA-treated group and 8 control males were used for the sperm production test.

Two independent larger-scale studies were subsequently conducted using the University of Missouri test conditions to determine if the reported results could be replicated. In both cases, the reported low-dose effects could not be replicated.

A study sponsored by the Society of the Plastics Industry, Inc. (SPI) and the European Chemical Industry Council (CEFIC) attempted to duplicate the original experimental conditions as closely as possible (Cagen *et al*, 1999). Although the SPI/CEFIC study employed more doses (0, 0.2, 2, 20 and 200 µg/kg body weight/day), more mice per group (28 females per treatment group and controls, all male offspring examined) and a greater number of endpoints than the original studies, no low-dose effects were observed.

Similarly, John Ashby and colleagues at the AstraZeneca Central Toxicology Laboratory in the United Kingdom (Ashby *et al*, 1999) also used the University of Missouri test methods to the extent possible, with the same BPA doses in CF1 mice. The findings reported by the vom Saal laboratory could not be replicated. Ashby and his coworkers found no statistically significant effects on prostate weight or efficiency of sperm

production.

Re-evaluation of the raw data from the SPI/CEFIC and Ashby studies by the NTP peer review Statistics Subpanel confirmed the results of both studies. In contrast, the effects reported by vom Saal (vom Saal *et al*, 1998) were not statistically significant and were not confirmed (NTP Report, 2001).

In a similar sequence of events, a group of researchers at the Freie Universität Berlin reported that exposure of pregnant Sprague-Dawley rats to 20, 100 or 50,000 µg/kg body weight/day of BPA for 16 days (gestation 6 through 21) led to a range of effects on the sexual development of the male and female pups at all doses. These results were presented in a series of abstracts (Chahoud *et al*, 2001; Fialkowski *et al*, 2000; Schönfelder *et al*, 2001; Talsness *et al*, 2000b, 2001) and one paper (Talsness *et al*, 2000a), which are not entirely consistent. However, none of the results could be replicated in either Sprague-Dawley rats or in another rat strain (Tinwell *et al*, 2002). In addition, re-evaluation by the NTP Statistics Subpanel revealed that concurrent controls were not used in the Chahoud study, which lead the NTP panel to conclude, "The lack of concurrent controls in this study was a serious design deficiency. This confounding of possible treatment effects with time-related changes precludes any reliable assessment." (NTP Report, 2001).

Weight of Scientific Evidence Shows the Low-Dose Hypothesis to be Unproven

The lack of low-dose effects in the definitive large-scale studies and the inability to replicate low-dose effects reported in small-scale studies demonstrates that the low-dose hypothesis for BPA cannot be valid. A series of independent expert bodies have comprehensively reviewed the evidence for and against low-dose effects and have consistently reached this same conclusion.

U.S. National Toxicology Program

In 2000, the U.S. National Toxicology Program (NTP) conducted an independent scientific peer review of the evidence for and against "low-dose endocrine disruptor" effects (NTP Report, 2001). This review was co-sponsored by the U.S. Environmental Protection Agency and the U.S. National Institute of Environmental Health Sciences. The peer review included a Statistics Subpanel, which re-evaluated the experimental design, data analysis and interpretation of results, and a Bisphenol A Subpanel, which reviewed all available studies on BPA. In regard to the studies that demonstrated the absence of low-dose effects of BPA, the Bisphenol A Subpanel concluded:

> "As a group these studies are very consistent, the conclusions are supported by appropriate statistical analyses, and the Statistics Subpanel confirmed the lack of BPA effects for the studies…" and "Collectively, these studies found no evidence

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> for a low-dose effect of BPA, despite the considerable strength and statistical power they represent, which the subpanel considered especially noteworthy."

In their overall conclusion, the Bisphenol A Subpanel stated:

> "There is credible evidence that low doses of BPA can cause effects on specific endpoints. However, due to the inability of other credible studies in several different laboratories to observe low dose effects of BPA, and the consistency of these negative studies, the Subpanel is not persuaded that a low dose effect of BPA has been conclusively established as a general or reproducible finding. In addition, for those studies in which low dose effects have been observed, the mechanism(s) is uncertain (i.e., hormone related or otherwise) and the biological relevance is unclear."

U. S. Environmental Protection Agency

The conclusions of the NTP peer review panel were further evaluated by the U.S. Environmental Protection Agency, leading to a statement on their view of the low-dose hypothesis (EPA, 2002). Significantly, EPA refers to the claimed low-dose phenomenon as still a "hypothesis", indicating their view it has not been proven. Because of this, EPA further stated, "it would be premature to require routine testing of substances for low-dose effects."

EC Scientific Committee for Toxicity, Ecotoxicity and the Environment

The European Commission has completed a comprehensive risk assessment on BPA, which includes a review of evidence for and against low-dose effects (EU, 2002). The European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2002) independently reviewed the Risk Assessment Report (RAR) and stated:

> "[A] number of studies using non-standard protocols have reported effects of bisphenol A administration on development using substantially lower doses than the studies performed according to testing guidelines. The RAR critically describes the many weaknesses (lack of repeatability, problems with experimental design and statistical evaluation, poor reporting) of the low dose studies. The CSTEE agrees with the conclusion of the RAR that there is no convincing evidence that low doses of bisphenol A have effects on developmental parameters in offspring and remarks that effects observed are not adverse."

The CSTEE further remarked, "a number of high quality studies on the reproductive and developmental effects of bisphenol A are already available and do not support low-dose effects."

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Japanese Ministry of Economy, Trade and Industry

Also in 2002, the Japanese Ministry of Economy, Trade and Industry released a hazard assessment of BPA (METI, 2002). In regard to the need for risk assessment or other measures, the Ministry stated:

> "Though it is necessary to collect further information on so-called 'low dose effects' represented by BPA from academic point of view, it seems unnecessary to take any specific measure other than the above, considering the view expressed by NTP Low Dose Effect Panel that the low dose effect of BPA at present is a phenomenon observed under considerably limited experimental conditions and it is hardly considered to be the general phenomenon."

Japanese Ministry of Health, Labor and Welfare

The Japanese Ministry of Health, Labor and Welfare has also recently released a report from an expert review committee that has been evaluating the potential risks of endocrine disrupting substances (MHLW, 2002). After evaluating experimental reports on low-dose endocrine disruption, the expert committee concluded, "no reproducible experimental results have been obtained, and at this point of time, it is doubtful whether we can conclude that there are endocrine disrupting effects in the low dose range."

Conclusion

The low-dose hypothesis for BPA has been thoroughly tested with a series of comprehensive, carefully conducted studies. Included are definitive large-scale studies as well as studies aimed at replicating the results of studies reporting low-dose effects. The consistent lack of low-dose effects found in these studies demonstrates that the low-dose hypothesis is not valid.

The weight of scientific evidence provided by these studies clearly supports the safety of BPA and provides strong reassurance that there is no basis for human health concerns from exposure to low doses of BPA.

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