MANUFACTURED CONTROVERSY REGARDING SOURCES OF EXPOSURE TO BPA AND MEASUREMENT OF BPA IN HUMAN SERUM

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Bisphenol A Research Needs: Determine Sources of Human Exposure

- Human data suggests continuous exposure:
  Oral (buccal/sublingual) and gastrointestinal:
  Food and beverages - can lining, packaging, storage containers.

  Transdermal: thermal paper
  Water - drinking, bathing

  Inhalation: associated with dust

  How many other unknown sources?
LEACHING OF BISPHENOL A INTO WATER FROM CANS AND A FOOD CONTAINER

Bisphenol A Concentration in Solution after 24 Hours

Talsness, Andrade, Kuriyama, Taylor, vom Saal
Phil. Trans. Royal Soc. B, 2009
Unconjugated (Bioactive) BPA

Liver enzyme UDP-glucuronosyltransferase

The hepatic portal system

BPA Glucuronide

95-99% of BPA swallowed or administered by gavage is conjugated; High first-pass metabolism

Taylor et al. EHP 2011
SOURCE OF CONTROVERSIES ABOUT ROUTES OF EXPOSURE TO BPA
The Panel concluded that injection studies ... would produce irrelevently high internal doses of the active parent compound, and would tend to produce “false positive” effects from the point of view of the human oral situation. The intent ... is to limit the impact of those studies...

Actual impact in adult – injection results in about 10-fold higher BPA.

Fred vom Saal, Public comment to CERHR Panel, November, 2007

The decision by the CERHR BPA panel to discount studies that did not involved feeding pregnant females or newborns is not supported by the published science.

The decision to disregard non-oral studies by 3 members of The CERHR panel (2 worked for industry) led to a significantly lower estimate of BPA hazard in the final NTP report on BPA.
PLASMA UNCONJUGATED BISPHENOL A IN NEONATAL MICE DOES NOT DIFFER AFTER FEEDING OR SUBCUTANEOUS INJECTION

Taylor et al 2008
Reprod. Toxicol.
Letter from CERHR Panel chair to Suzanne Rust regarding the findings reported in Taylor et al 2008 and the panel’s decision to disregard non-oral studies.

Robert Chapin, the chairman of the CERHR BPA panel, and an executive at Pfizer, said: the new research "stands in contrast to a number of other studies that show the opposite." He said it was those other studies that led us to the logical conclusion we reached.” When asked to supply the citations for those studies, he said he could not remember them offhand.
Effects of Life Stage

PREDICTION:

• There is a low rate of metabolism of BPA in early life

BPA Expert Panel Consensus Statement
Sponsored by: NIEHS / EPA
Chapel Hill, NC, November 2006
vom Saal et al. Reprod. Toxicol. 2007
“The EFSA Panel considers that there is sufficient capacity in the neonate to conjugate BPA at doses below 1 mg/kg bw.”

(Primary consultant and EFSA Panel member: Wolfgang Dekant; Paid by: Polycarbonate/BPA Global Group)

LETTER TO EFSA (2008)

This argument of the Panel ... cannot be accepted at all.

Dr. Andreas Gies, Director, Environmental Health German Environment Agency
“The high blood levels for free BPA reported in these [biomonitoring] studies are not consistent with ... estimated levels of exposure through the diet by EFSA.”

[the biomonitoring studies referred to by EFSA were later reviewed by Vandenberg et al. EHP 2010]
“The participants commented that the model used in the EFSA risk assessment was not consistent with the current experimental data and therefore consideration should be given to modifying the model.”

A. Gies, B. Heinzow, H. Dieter and J. Heindel
BISPHENOL A IN URINE OF PREMATURE INFANTS, CHILDREN, ADOLESCENTS AND ADULTS (CDC)

Total BPA (ng/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU</td>
<td>(3.6-5.1)</td>
</tr>
<tr>
<td>Child</td>
<td>(2.5-3.1)</td>
</tr>
<tr>
<td>Adolescent</td>
<td>(1.6-2.3)</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
</tr>
</tbody>
</table>

(1.6-946 = Min - Max)

Calafat et al. 2008, 2009
Env. Health Perspect.

NICU: Neonatal Intensive Care Unit
FDA STUDY OF SERUM BPA AFTER AN ORAL GAVAGE DOSE

Abstract: “No age-related changes were seen in internal exposure metrics for aglycone [unconjugated] BPA in monkeys.”

Area under the plasma concentration curve

Young monkeys have higher internal exposure to free BPA

4-fold higher serum BPA in PND-5 infants than in adults

Doerge
Twaddle
Woodling
Fisher
TAP 2010
Do Not Believe What You Read in the Abstract!

• “We have learned that newborn and young rodents have significant age-dependent differences in metabolic capabilities, resulting in their not being able to metabolize BPA as well as adult rodents do and thus being exposed to higher levels internally; this is not the case for nonhuman primates (Doerge et al. 2010).”

Birnbaum et al. EHP Editorial July, 2013
ESTIMATE UNDETECTABLE UNCONJUGATED BPA IN HUMAN SERUM BASED ON BACK-CALCULATION FROM URINE TOTAL BPA AND ALL EXPOSURE TO BPA MODELED BY GAVAGE

Review
Human exposure to bisphenol A by biomonitoring: Methods, results and assessment of environmental exposures
Wolfgang Dekant a,*, Wolfgang Völkel b

a Department of Toxicology, University of Würzburg, Germany
b Bavarian Health and Food Safety Authority, Environmental Medicine/Biomonitoring, Munich, Germany
Received 5 September 2007; revised 27 November 2007; accepted 2 December 2007
Available online 14 December 2007

Bisphenol A (BPA) daily intakes in the United States: Estimates from the 2003–2004 NHANES urinary BPA data

JUDY S. LAKIND a AND DANIEL Q. NAIMAN b

a LaKind Associates, LLC, Catonsville, Maryland, USA
b Department of Applied Mathematics and Statistics, The Johns Hopkins University, Baltimore, Maryland, USA

This work was supported by the Polycarbonate/BPA Global Group.
BPA Absorption and Bioavailability

These can only be determined by measuring unconjugated BPA in serum not by back-calculating and estimating from total BPA in urine.

• **Absorption**: movement of BPA from the site of administration into the blood which drains the site of administration.

• **Bioavailability**: the amount of BPA which actually gains access to the systemic (arterial) circulation without being metabolized.
There was no evidence of BPA contamination in assay or field blanks collected alongside the biological samples.


PUBLISHED STATEMENTS THAT HUMAN SAMPLES ARE CONTAMINATED WITH ENVIRONMENTAL BPA ARE FALSE
“A significant body of evidence has shown that contamination from ubiquitous environmental sources of BPA during sample collection, storage, and analysis has a propensity to introduce artifactual aglycone BPA in extracts from blood and tissues.”

References Cited
Doerge et al., 2012; Koch et al., 2012; Markham et al., 2010;
Salgueiro-González et al., 2012; Teeguarden et al., 2011;
Twaddle et al., 2010; Vandentorren et al., 2011; Völkel et al., 2002

Bioavailability in Plasma of BPA by sublingual, gavage (oral) or IV administration in dogs

<table>
<thead>
<tr>
<th></th>
<th>Oral 20 mg/kg</th>
<th>Sublingual 50 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability %</td>
<td>0.72 ±0.28</td>
<td>100%</td>
</tr>
<tr>
<td>(from BPA AUCs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorption %</td>
<td>54 ±19</td>
<td>90 ±26</td>
</tr>
<tr>
<td>(From BPA-gluc AUCs)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:
A very high ratio of conjugated BPA / unconjugated BPA in blood is only seen after gavage administration.

V. Gayrard et al. EHP 2013
Buccal/Sublingual absorption

Buccal/Sublingual absorption is similar to IV injection and bypasses the hepatic first-pass conjugation effect.

- sublingual (SL) = under tongue
UNCONJUGATED AND TOTAL BISPHENOL A IN SERUM FROM 33 ADULTS IN THE USA

2.82±0.43 Urine Total BPA (μg BPA / g Creatinine)

Estimate – 92% of exposure was not from GI absorption

\[
\frac{\text{BPA-G}}{\text{uBPA}} = 5.7
\]

<table>
<thead>
<tr>
<th>Concentration (ng/ml)</th>
<th>Unconjugated</th>
<th>Total ( Conj + Unconj )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.91±0.30</td>
<td>6.10±0.97</td>
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Taylor et al. unpublished
Commonweal study – Is it in Us 2008
QUESTION
WHAT IS A NON-ORAL SOURCE OF EXPOSURE TO BPA THAT
EXPLAINS THE HIGH BLOOD LEVELS OF UNCONJUGATED BPA
BEING REPORTED IN BIOMONITORING STUDIES?
BISPHENOL A - BPA

BISPHENOL S - BPS
BPA and BPS Extracted from Thermal Receipts

<table>
<thead>
<tr>
<th>Chemical in paper</th>
<th>mg/g receipt</th>
<th>mg/8×12 cm receipt</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPA-positive (44%)</td>
<td>19.6±1.0</td>
<td>9.0±0.4</td>
</tr>
<tr>
<td></td>
<td>(11.5–26.3)</td>
<td>(6.1–11.3)</td>
</tr>
<tr>
<td>BPS-positive (52%)</td>
<td>23.5±0.7</td>
<td>10.8±0.3</td>
</tr>
<tr>
<td></td>
<td>(15.2–30.1)</td>
<td>(7.1–13.2)</td>
</tr>
</tbody>
</table>
BPA USED AS A DEVELOPER IN THERMAL PAPER

Thermal Paper

Thermal head

Thermal reactive layer
Developer (Free BPA)

Dye

Precoat

Base paper

Hormann et al.
Plos One, 2014
PERSONAL CARE PRODUCTS CONTAIN
DERMAL PENETRATION ENHANCING CHEMICALS

ALSO IN:
Handcreams
Sunscreens
Soaps
My Hand After Using Hand Sanitizer and Holding a Thermal Receipt
BPA Transferred to Dry Hands or Wet Hands After Using Hand Sanitizer

A. WET HANDS

B. DRY HANDS

μg BPA removed from hand

Holding time (sec)

Hormann et al.
Plos One, 2014
BPA Transferred from Hands to 10 French Fries After Using Hand Sanitizer

Hormann et al.
Plos One, 2014
SERUM BPA AFTER USING HAND SANITIZER AND HOLDING THERMAL PAPER THEN HOLDING AND EATING 10 FRENCH FRIES

Time after eating fries (min)  
Concentration (ng/ml)

Ratio  
\( \text{uBPA/BPA-G} = 0.85 \pm 0.33 \)

Hormann et al. Plos One, 2014
**HUMAN BLOOD LEVELS OF BPA**

- Most humans are exposed to BPA
- Mean levels in adults and fetuses are 1 - 3 ppb (1 - 3 ng/ml or 4 - 13 nM)

[Thermal receipts – average serum uBPA = 4 ng/ml]

These levels are higher than levels that cause adverse effects in human and animal cells and in animal experiments.

Components of Chemical Risk Assessments

1. Hazard assessment
2. Dose-response evaluation
3. Exposure assessment
4. Risk characterization
5. Risk management

EXPOSURE ASSESSMENT

Current Practice:
Routes of exposure not known for chemicals used in many products (confidential information).

Need:
Public disclosure of chemicals used in products
CONCLUSIONS

◆ The estimates of total daily BPA exposure by regulatory agencies have not taken into account dermal exposure from thermal receipt paper or sublingual absorption as major exposure routes.

◆ The equipment we used used to collect blood and urine in an accredited medical facilities is not a source of contamination of BPA. [ONLY THE FDA HAS A CONTAMINATED ASSAY]

◆ The levels of serum unconjugated BPA due to holding thermal paper are in the range associated with diseases that have been increasing over the last few decades.