ANNEX B: CLH PROPOSAL CONTAINS INCONSISTENT AND INCORRECT INFORMATION ON TYL ET AL. (2002 AND 2008A)

The Tyl et al. (2002 [1] and 2008a [2]) multi-generational studies of BPA in rodents are widely regarded as authoritative research on BPA reproductive effects. These studies have been repeatedly relied upon by governmental regulators in assessing the risks and hazards of BPA. Tyl et al. (2002 and 2008a) have been credited for their statistical power, wide range of doses and adherence to established guideline protocols. The 2008 European Risk Assessment Report (EU RAR) said:

> *"…We consider this investigation by Tyl et al. (2007) as the gold-standard, definitive study of the reproductive toxicity of BPA (for the endpoints examined)…. [3]*

Likewise, the FAO/ WHO report said that:

> *"Typically, a dose of 5 mg/kg bw per day has been identified as a NOAEL in assessments conducted for regulatory or health-based guidance value setting purposes, based on consideration of two multigeneration studies in rats and mice conducted by Tyl et al. (2002, 2008a). These studies are generally considered to be statistically and methodologically sound for the end-points investigated and have sufficient dose groups to support dose–response modeling." [4]*

Tyl 2002 was described by, NTP (2001) as *"arguably the most comprehensive of the studies we evaluated."*[5]

In contrast to these highly-regarded guideline studies, many of the reproductive studies relied upon by the CLH proposal are non-guideline, exploratory studies with significant methodological weaknesses, NTP-CEHRH (2008)[6] evaluated many of these publications, and identified concerns such as lack of statistical power and non-oral dosing. For more detail, see Annex A of our Comments.

Because the Tyl studies are so central to the body of research and standard setting on BPA, criticisms of those studies must be taken seriously and evaluated for accuracy and plausibility.

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[1] Tyl et al. (2002), *Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats*, Toxicological Sciences, Volume 68, Issue 1, Pp. 121-146 (2002).

[2] Tyl et al. (2008a), *Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice*. Toxicol. Sci. 104(2), 362–384, 2008.

[3] European Commission, Joint Research Centre, Institute for Health and Consumer Protection, *Updated Risk Assessment of 4, 4 Isopropylenedephenol (Bisphenol-A), Human Health Addendum*, April 2008, p. 87.

[4] Food and Agriculture Organization of the United Nations, the World Health Organization, *Joint Expert Meeting to Review Toxicological and Health Aspects of Bisphenol A: Summary Report*, November 1-5, 2010, available on the web at: ftp://ftp.fao.org/ag/agn/agns/BPA_Summary_Report.pdf, p. 28.

[5] National Toxicology Program, *Report of the Endocrine Disruptors Low Dose Peer Review*, page 1-11, August 2001.

[6] Center for the Evaluation of Risks to Human Reproduction, *NTP-CERHR monograph on the potential human reproductive and developmental effects of bisphenol* NIEHS, Research Triangle Park, Sept. 2008 .

The CLH Proposal[7] mischaracterized important elements of the Tyl et al. 2008a study on CD-1 mice .

Study Data Demonstrate Evidence of Systematic Toxicity and No Effects on Fertility

> Page 37: "*No toxicity was observed in the F0 or F1 generations and effects on the fertility were only observed at the highest dose (3500 ppm: 600 mg/kg bw/d). Although it has been described in the paper that systemic toxicity can be observed at this dose, a thorough observation of the data provided as supplementary tables with the paper did not allow validating this statement."*

The Tyl et al. 2008a publication provides detailed tables for each dose showing the decreased mean adult male body weights and weight gains (see Supplementary Tables 1 (F0), 2 (F1), and 3 (F1 retained) and mean adult female body weights and weight gains (see Supplementary Tables 4–6 (F0 prebreed, gestation, lactation) and 7–9 (F1 prebreed, gestation, lactation)).

The authors did not identify fertility effects from this data, even in the presence of systemic toxicity. The European RAR adopts a similar interpretation of the data, stating that:

> *"In the mouse 2-generation study, using dose levels of 0.003-600 mg/kg/day, no effects on fertility, reproductive organ weights and histopathology or sperm production were observed."* [8]

Further, the fertility effects claimed by the CLH proposal relate to a dose level that the authors and key reviewers have linked to systemic toxicity. For example, this interpretation of the data is relied upon by the EU RAR, which identified significant effects on bodyweight gain, kidney and liver (including centilobular hepatocyte hypertrophy and renal pathology in F0/F1 males) at the 600 mg/kg/day dose. All of these parameters are evidence of systemic toxicity, which led EU RAR to establish the NOAEL at the next lowest dose of 50 mg/kg/day.

Overall, there was no effect on fertility in the Tyl et al. 2008a study and the statement that validation of the systemic toxicity data is not possible is not credible because the Supplementary Tables demonstrate reduced body weight and body weight gain. In addition to body weight, there was increased liver and kidney weights, centrilobular hepatic hypertrophy and renal pathology in F0/F1 males, all of which provide evidence of systemic toxicity.

[7] ANSES (on behalf of the French MSCA), *CLH Report: Proposal for harmonized Classification and Labelling of Bisphenol A*, 17 July, 2013.

[8] European Commission, Joint Research Centre, Institute for Health and Consumer Protection, *Updated Risk Assessment of 4, 4 Isopropylenedephenol (Bisphenol-A), Human Health Addendum*, April 2008, p. 128.

Increased Kidney and Liver Weight and Histopathological Changes Are Indicative of Systemic Toxicity

> Page 38: "*Signs of toxicity were observed as increased kidney and liver weight from 300 ppm and onward for F0 males, from 0.018 ppm in F1 parental males, in F0 and F1 females and in F1 & F2 pups (male and females) at 3500 ppm. However, these results suggest rather a strong and direct effect of BPA on these organs than systemic toxicity."*

Effects on kidney and liver (at least in the F0 generation) were considered by the authors and key reviewers to be systemic toxic effects.

This interpretation of the data is relied upon by the EU RAR 2008, which defined the NOAEL for general toxicity at 50 mg/kg/day on the basis of the observation of toxicologically significant effects on bodyweight gain, kidney and liver at the next highest dose level of 600 mg/kg/day (3500 ppm). The EU RAR noted that:

> *"Evidence of general toxicity was observed in 300 ppm and 3500 ppm groups. At 300 ppm, this evidence was limited to an increased incidence of centrilobular hepatocyte hypertrophy of minimal to mild severity in F0 males (40% vs. 11% in controls) and females (10% vs. 2%) and F1 parental/retained males (30% vs. 10%). There were no increases in liver weight at this dose level. At 3500 ppm, bodyweight gain was reduced among the F1 parental/retained males; at termination mean bodyweights of the parental and retained males were 4% and 10%, respectively, less than the vehicle controls. Kidney weights were increased in F0 males and in F1 parental/retained males. Histological examination of the kidney revealed an increased incidence of minimal to mild nephropathy in the F0 males and F1 parental/retained animals at 3500 ppm. Absolute liver weights were significantly increased in F0 males (by 18%) and females (by 20%) and in F1 parental males (by 17%) at 3500 ppm. Histological examination of the liver revealed an increased incidence of minimal to mild centrilobular hypertrophy in the F0 males (100% vs. 11% in controls) and females (60% vs. 2%) and F1 parental/retained males (65% vs. 10% in controls) and parental females (70% vs. 4%) at 3500 ppm. The increased incidence of centrilobular hypertrophy at 300 ppm (50 mg/kg/day) was not accompanied by an increase in the group mean liver weight, suggesting that the liver changes seen at this dose level were minor and without toxicological significance. Therefore, the study NOAEL for general toxicity can be set at 50 mg/kg/day on the basis of the observation of toxicologically significant effects on bodyweight gain, kidney and liver at the next highest dose level of 600 mg/kg/day (3500 ppm)."* [9]

Contrary to the assertions of the CLH proposal, increased kidney and liver weight observed in the Tyl et al. 2008a study were indicators of systemic toxicity.

[9] European Commission, Joint Research Centre, Institute for Health and Consumer Protection, *Updated Risk Assessment of 4, 4 Isopropylenedephenol (Bisphenol-A), Human Health Addendum*, April 2008, p. 74.

Treatment Related Pituitary Effects Were Not Observed in Tyl et al. 2008a or in the EU RAR Review of That Study

The CLH proposal concluded based on Tyl et al. 2008a that BPA exposure impacts the pituitary gland after an in utero exposure.

> Page 38: *"Together with the effect of BPA on BW evolution depending on the sex of the animals, another finding points out the potential endocrine effect of BPA: Pituitary relative weight is increased in F1 parental and retained male at all doses (significant at 300 ppm). Only F0 E2-treated males have this finding. Detailed brain dissection was not performed and brain global was weighted in pups, so we cannot confirm this finding in the next generation. Therefore, BPA exposure impacts the pituitary gland after an in utero exposure that might affect fertility through sexual hormone modifications."*

In fact, no treatment related effect of BPA on pituitary is noted in the publication by the authors. As the supplementary data provided by Tyl et al. 2008a (reproduced below) indicate, there is no significant observation in F0 males on pituitary (absolute weight, weight relative to body weight and brain weight). In F1 adults, a significant increase is observed at 3500 ppm (weight relative to body weight), but no significant effects are observed for absolute weight or weight relative to brain weight. In F1 retained adults, significant increase in absolute pituitary weight is seen at 300 ppm (no significant observation at 3500 ppm) and increase in pituitary weight relative to body weight is seen at 3500 ppm (no significant observation relative to brain weight). There is no significant observation in F0 or F1 females on pituitary (absolute weight, weight relative to body weight and brain weight);

The CLH proposal at page 38 correctly observes that relative weight of the pituitary is increased in some dose groups. However, this suggests that the measured weights are not treatment related, because no dose response could be observed over the whole dose range of the study.

Overall, the statement that *"BPA exposure impacts the pituitary gland after an in utero exposure"* in this study is not supported by the data reported in Tyl et al. 2008a; no treatment related effect of BPA on pituitary is mentioned in the EU RAR.

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0[a]	0.018	0.18	1.8	30	300	3500	0.5

F0 males:

Relative Pituitary Weight (% of sacrifice weight)[b]								
	0.0069 ‡‡‡	**0.0067**	**0.0070**	**0.0066**	**0.0066**	**0.0070**	**0.0074**	0.0079 ***
	± 0.0001	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002
	N=54[e]	N=28	N=27[e]	N=28	N=26[e]	N=26[e]	N=27[c]	N=28

F1 males

Relative Pituitary Weight (% of sacrifice weight)[e]								
	0.0067 ‡‡‡	**0.0066**	**0.0063**	**0.0065**	**0.0070**	**0.0065**	**0.0074 ***	0.0077 ***
	± 0.0001	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002
	N=52[i,j,n]	N=23[j,n]	N=27	N=28	N=25[j]	N=27[g]	N=26[j]	N=28

Retained F1:

Relative Pituitary Weight (% of sacrifice weight)[c]

	0.0063 ‡‡‡	**0.0062**	**0.0066**	**0.0066**	**0.0067**	**0.0068**	**0.0073 *****	0.0073 ***
	± 0.0001	± 0.0001	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002	± 0.0002
	N=47[e,f]	N=27	N=21[e]	N=24[e]	N=25[e]	N=21	N=22	N=19

F0 Males

Relative Pituitary Weight (% of brain weight)[b]							
0.5292	0.5142	0.5314	0.5161	0.5204	0.5413	0.5521	0.5848
± 0.0124	± 0.0167	± 0.0175	± 0.0174	± 0.0163	± 0.0181	± 0.0142	± 0.0188
N=53[d,e]	N=28	N=27[e]	N=28	N=26[e]	N=26[e]	N=28	N=28

F1 males

Relative Pituitary Weight (% of brain weight)[e]							
0.5045 ‡‡‡	0.5067	0.4860	0.4850	0.5206	0.4706	0.5415	0.5511
± 0.0108	± 0.0129	± 0.0168	± 0.0120	± 0.0149	± 0.0133	± 0.0181	± 0.0143
N=53[i,j]	N=24[j]	N=26[h]	N=28	N=25[j]	N=28	N=25[h,j]	N=27[h]

Retained F1

Relative Pituitary Weight (% of brain weight)[c]							
0.4908 ‡	0.5087	0.5237	0.5275	0.5312	0.5414	0.5299	0.5596 **
± 0.0089	± 0.0143	± 0.0162	± 0.0157	± 0.0159	± 0.0127	± 0.0187	± 0.0185
N=45[d,e,f]	N=27	N=21[e]	N=24[e]	N=25[d,e]	N=21	N=22	N=17[d]

Extended Estrus Was Not Observed in F0 Mice in Tyl et al. (2008a)

The CLH proposal incorrectly cites Tyl et al. 2008a in support of the claim that F0 females experienced extended periods of estrus:

> Page 38: *"At this dose, BPA exposure increased the length of the gestation by 0.3 days, reduced the body weight of the pups during lactation, and F0 treated females were twice more in estrus compared to controls as shown in the supplementary table 22 p. 6/7, line 5."*
>
> Page 54: *"F0 treated females were twice more in estrus as compared to controls at 600 mg/kg."*

As shown in the supplementary data in Tyl et al. 2008a on estrus (reproduced below), the data do not show a clear pattern of extended estrus among treated females. There were no statistically significant findings in the number of F0 or F1 females in estrus at any dose when compared to controls. Also, the study author concluded that *"stage of estrus at demise was unaffected in mice"*.

Overall, no statistically significant association in F0 or F1 females is reported and consequently no treatment related effect can be considered.

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0[a]	0.018	0.18	1.8	30	300	3500	0.5
F0 females:								
Number in Estrus	10	9	6	10	8	9	9	10
Percent in Estrus	17.86	32.14	22.22	37.04	29.63	32.14	32.14	35.71
F1 females:								
Number in Estrus	15	11	6	7	5	5	10	8
Percent in Estrus	27.27	39.29	22.22	25.93	19.23	18.52	37.04	28.57

Extended Diestrus Was Not Observed in Tyl et al. 2008a

The CLH proposal also claims that extended periods of **diestrus** were observed in the Tyl et al. 2008a study.

> Page 53: "*It has been demonstrated that not only extended periods of estrus were seen, but also extended period of diestrus (Rubin et al., 2001; Mendoza-Rodriguez et al., 2011; Nikaido et al., 2004; Honma et al., 2002; Tyl et al., 2008a)*."

As the table on diestrus in Tyl et al. 2008a (reproduced below) clearly shows, for both the F0 and F1 females, the percentage in diestrus was notably uniform across the dosing groups and the control group and there were no statistically significant differences noted for any BPA treatment group.

The data in Tyl et al. 2008a does not support the CLH proposal's statement on extended period of diestrus.

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0[a]	0.018	0.18	1.8	30	300	3500	0.5
VAGINAL CYTOLOGY EVALUATION AT NECROPSY:[q]								
F0 females:								
Number in Diestrus	39	15	18	17	18	17	17	7
Percent in Diestrus	69.64 **£**	53.57	66.67	62.96	66.67	60.71	60.71	25.00 **ΦΦΦ**
F1 females:								
No. in Diestrus	40	17	20	17	19	21	17	17
Percent in Diestrus	72.73	60.71	74.07	62.96	73.08	77.78	62.96	60.71

There is no scientific evidence that CD-1 mice are insensitive to estrogenic compounds

> Page 95: *"Many published findings reporting effects of very low doses of positive control estrogens and BPA in CD-1 mice (Myers et al., 2009) demonstrate that the CD-1 mouse was somehow rendered insensitive in the test system used by Tyl et al. (2008a)."*

Although the CLH proposal mentions Myers et al. 2009, publications refuting Myers' claims of estrogenic insensitivity are not discussed. These include EFSA (2010)[10]; CERHR (2008); Gray et al. 2010[11]; and Tyl 2009.[12] Significantly, the CLH proposal does not reference Tyl 2009, published later in the same year as Myers 2009. In that publication, Dr. Tyl's response shows that the test system used in Tyl et al. 2008a was sensitive:

> *"We identified the same BPA systemic and reproductive/developmental NOAELs (and sensitivity comparable to similar dietary E2 intakes) in rats and mice, with no BPA effects on the prostate weight or histopathology. Strain differences in response to estrogens in rats (and*

[10] European Food Safety Authority (EFSA), EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF), *Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A*. EFSA Journal 2010; 8(9):1829, available on the web at: http://www.efsa.europa.eu/en/efsajournal/doc/1829.pdf.

[11] Gray et al, *Rebuttal of "Flawed Experimental Design Reveals the Need for Guidelines Requiring Appropriate Positive Controls in Endocrine Disruption Research" by Vom Saa1 (2010).* Toxicological Sciences 115, 614-620, 2010

[12] Tyl, R.W., *Basic Exploratory Research Versus Guideline-Compliant Studies Used for Hazard Evaluation and Risk Assessment: Bisphenol A as a Case Study*, Environmental Health Perspectives 117, 1644-51, 2009

mice) vary across tissues, so no strain can be considered more sensitive than another (Howdeshell et al. 2008).

E2 activities via estrogen receptor-α in the reproductive tract did not display major strain differences in OECD multilaboratory rat uterotrophic assay validation studies; oral BPA was only a weak partial agonist at 400–600 mg/kg/day (Kanno et al. 2003)."

Importantly, the Tyl et al. 2008a study was conducted under the supervision of a Steering Group of experts from the EU member states and was chaired by a representative of the European Chemicals Bureau. The design of the study, as well as its results and conclusions, were subsequently relied upon by the EU RAR.[13] The study also included a concurrent positive control of 17β-Estradiol (0.5 ppm), which clearly demonstrated estrogenic responses in this mouse model. Prior to this study, a two-generation reproduction study was conducted in the CD-1 mouse using a wide range of doses of 17β-Estradiol (Tyl et al., 2008b). This study also demonstrated a number of estrogenic effects in the CD-1 mouse model.

Overall, relevant information that address potential species and strain differences is not included in the CLH proposal. In conclusion, there is no scientific evidence that CD-1 mice are insensitive to estrogenic compounds. In fact, there is ample evidence to support that the CD-1 mouse is responsive to estrogenic compounds.

The CLH proposal mischaracterized important elements of the Tyl et al. 2002 study in Sprague Dawley (SD) rats.

There is no evidence that Sprague Dawley Rats are insensitive to estrogenic compounds

Page 53:

"Kwon et al. hypothesize that this lack of effect may be due to insensitivity of Sprague-Dawley rats to endocrine-mediated toxicity. This is confirmed by the Tyl et al. study (Tyl et al., 2002)."

Page 60:

"The relatively marginal data obtained from the 2 key multigeneration studies (Tyl et al. 2002 et Ema et al., 2001) could be explained by the low sensitivity of SD rats to estrogenic coumpounds. (Kwon et al., 2000)."

The statement that Tyl et al. 2002 or Ema et al. 2001 confirm insensitivity of SD rats is incorrect. Relevant publications that address potential species and strain differences are not included in the CLH proposal. These include: EFSA (2010); CERHR (2008); Tyl et al. 2006**;** Gray et al. 2010; and Tyl 2009. In fact, the contrary conclusion is strongly suggested by Tyl et al. 2002, Tyl 2006, Tyl 2008a, and Tyl 2009. Recently, the U.S. Food and Drug Administration completed a sub-chronic neurobehavioral and neuroanatomical developmental study in SD rats[14] using a wide range of BPA doses and a concurrent positive control (EE2). The EE2 concurrent positive control in this study showed clear indications of estrogenic response.

Overall, there is no solid scientific evidence that SD rats are insensitive to estrogenic compounds. In fact, there is clear evidence to support that Sprague Dawley rats are responsive to estrogenic compounds.

[13] See European Commission, Joint Research Centre, Institute for Health and Consumer Protection, *Updated Risk Assessment of 4, 4 Isopropylenedephenol (Bisphenol-A), Human Health Addendum*, April 2008, p. 88.

[14] US National Center for Toxicological Research (NCTR), *Evaluation of the toxicity of Bisphenol A (BPA) in Male and Female Sprague-Dawley Rats Exposed Orally from Gestation Day 6 through Postnatal Day 90*, Technical Report of this study (Report Number: 2176.01; dated March 4, 2013).

Renal tubular degeneration and chronic hepatic inflammation in SD rats are not reproductive effects, but the product of systemic toxicity

The CLH proposal states on page 40:

> *"Although the data available for this study are less detailed than for the study above, we can affirm from the previous study that the slight to mild renal tubular degeneration and chronic hepatic inflammation observed in females for the three generations at 750 and 7500 ppm is a strong and direct effect of BPA on these organs rather than systemic toxicity."*

Similar to the multi-generation mouse study conducted on BPA by Tyl et al.2008a, the study in rats showed similar findings on the kidney and liver that were judged by the author and the EU RAR to be systemic toxic effects.

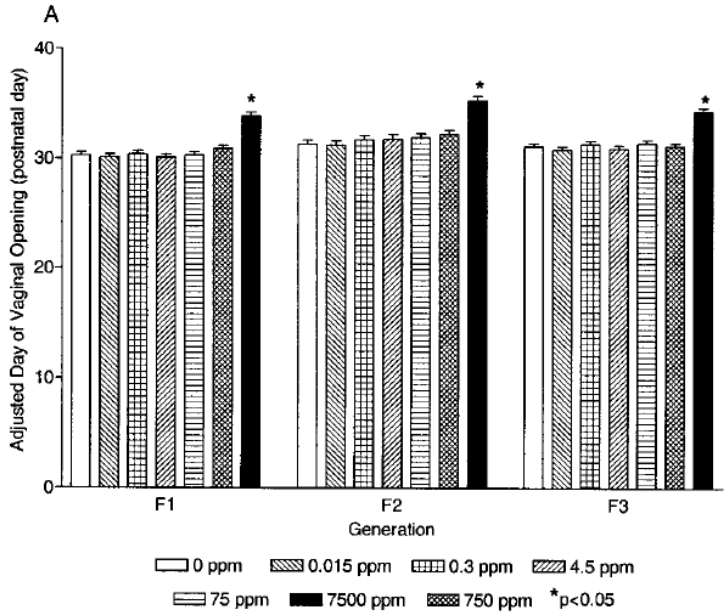
Overall, Renal tubular degeneration and chronic hepatic inflammation are not reproductive effects, but the product of systemic toxicity

Onset of Puberty is Not Affected at 50 mg/kg/day in SD Rats

Table 10 page 52:

> *"The absolute age at puberty (evaluated by the age at vaginal patency) was delayed in the F2 generation at 50 mg/kg and in the F1, F2 and F3 generations at 500 mg/kg."*

This statement is not correct. As shown in Tyl et al. 2002; Fig 7 (reproduced below), no significant observation is reported at 50 mg/kg.



Tyl et al. 2002 does not demonstrate effects on sperm concentration and accessory sex organs

Page 94: The CLH proposal states:

> *"Exposure to 3500 ppm of BPA decreased the epididymal sperm concentration in F0 male. A decreased paired testis weight (-17% compared to control) was observed in 3500 ppm F1 male pups (also observed in F2 male pups as relative testis weight/brain) together with decreased paired epididymal weight in 3500 ppm F1 parental male (-7% compared to control).*

In F2 male pups, the seminal vesicle coagulating gland weight was also decreased at all doses and significantly at 3500ppm (Tyl et al., 2002)."

Tyl et al. 2002 reported that there were no treatment-related effects on sperm measures or accessary sex organs. They specifically state:

"There were no effects of treatment in F0, F1, or F2 males on mating or fertility indices, or treatment- or dose-related direct effects in F0, F1, F2 and retained F3 males on absolute or relative weights of the testes, epididymides, prostate, or seminal vesicles plus coagulating glands. Also, there were no effects on epididymal sperm concentration (except for a significant reduction in epididymal sperm concentration in F1 males, but not F0, F2, and F3 males, at 7500 ppm), percent motile or progressively motile sperm, testicular homogenization-resistant spermatid head counts, DSP (except for a significant reduction in DSP at 7500 ppm for F3 males, but not F0, F1, or F2 males, with no effect on efficiency of DSP), or efficiency of DSP. Percent abnormal sperm was also unaffected for all F0, F1, F2, and F3 males in all groups. The slightly higher (but not statistically significant) values for F2 males at 0.015, 0.3, 4.5, and 75 ppm and for F3 males at 0.015 and 75 ppm were due to 1 or 2 males per group with few or no motile sperm and most or all abnormal sperm. In all cases for the F2 males, the affected males sired live litters (F3 males were not bred). There were no treatment-related gross or microscopic findings on reproductive organs for F0, F1, F2, or F3 adult males or females."

Overall, Tyl et al. 2002 does not report treatment-related effects associated with sperm concentration and accessory sex organs.

Conclusion

In conclusion, the CLH proposal makes inconsistent and incorrect statements about the multigenerational reproductive studies on rats (Tyl et al. 2002) and mice (Tyl et al. 2008a).

These include claims that fertility effects and increased kidney and liver weight in Tyl et al. 2008a were reproductive effects, when the data and interpretation of those data reveal these to be the result of systemic toxicity. The CLH proposal likewise claims that BPA caused pituitary effects in Tyl et al. 2008a, but study data suggests these effects are not treatment related. The CLH proposal cites Tyl et al. 2008a as supporting claims of extended estrus and diestrus, but the study data does not support these claims. Further, contrary to claims made in the CLH proposal, there is no scientific evidence that CD-1 mice or SD rats are insensitive to estrogenic compounds. In fact, the data clearly demonstrate that they are able to show indicators of response to estrogenicity.

Contrary to claims in the CLH proposal, as with the mouse model, renal tubular degeneration and chronic hepatic inflammation observed in rats are also indicators of systemic toxicity. The CLH proposal that delayed puberty is observable in Tyl et al. 2002 is not supported by the data. Observations about sperm concentration and accessory sex organs are not consistent across the generations, and therefore not considered by the study authors to be treatment related.

The Tyl studies, together with the weight of scientific evidence, demonstrate that BPA is not a selective reproductive toxicant, and that the proposed reclassification to Category 1B is not justified.

References:

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