10 Selected Phthalate Esters - SAB Reproductive/Developmental Review Summary - September 2015

		Reproductive and Developmental Effects	Other Effects Noted During Review			
Phthalate Ester	**Carbon Chain length range**	**Reproductive/Developmental =** Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in offspring *(UN GHS 2003)* [OSHA 2015].	**Liver**	**Endocrine**	**Other**	**Comments**
DAP - Diallyl phthalate - #131-17-9	C3	NOAEL for reproductive effects *(DAP Consortium, 2004)* was 50 mg/kg/day for dystocia (difficult labor) **[CPSC 2011b]** Prenatal toxic effects at 200 and 250 mg/kg/day - decreased fetal body weight and bone growth delay at 250 mg/kg/day; Developmental NOAEL at 150 mg/kg/day based on fetal weight changes and increased incidence of fetal skeletal variations; *No evidence of teratogenicity up to 250 mg/kg/day, no adverse effect seen at 150 mg/kg/day;* DAP showed a developmental toxicity that differed from DIBP. Impacts to fetus due to maternal toxicity @ 200 mg/kg/day or higher; Carbon backbone length alone does not predict developmental effects **[Saillenfait 2008]** *Uterine tumor effects (negative correlation - control highest)* **[NTP 1983]**	Liver effects in rats NOAEL @ 50 mg/kg/day based on histopathological findings *(NTP, 1985)* . **[CPSC 2011b]** Hepatotoxic effects and maternal effects with a NOAEL of 50 mg/kg **[Saillenfait 2008]** DAP also caused hepatocellular necrosis and hepatic fibrosis or cirrhosis in both sexes of rats at 200 and 400 mg/kg; *no liver lesions were observed in the DAP-treated mice.* **[Kluwe 1986]**	Ortho isomer of diallyl phthalate most potent (3x more potent than di-n-propyl) in binding to estrogen receptor due to hydrophobic interaction. **[Nakai 1999]**	*2-yr assay in mice (NTP, 1983) does not provide evidence that DAP is carcinogenic to mice* **[CPSC 2011b]** Papillomas of the forestomach in mice, as well as gastric hyperplasia and chronic gastric inflammation; Also related to an increased occurrence of mononuclear cell leukemia in female rats and equivocal increase in the occurrence of lymphomas in male mice **[Kluwe 1986]**	The lipophilic nature and long half life of alkyl phthalates may allow them to accumulate and persist in fatty tissues of the body thus increasing their concentration and bioavailability. **[Nakai 1999]**
DMEP - Bis(2-methoxyethyl) phthalate - #117-82-8	C3	Causes severe reproductive toxicity in adult animals: testicular atrophy; sperm damage; decreased testicular weight *(Kodak 1984, Cassidy et al. 1983);* Causes severe teratogenicity (severe skeletal malformations) in utero *(Parkhie et al. 1982, Singh et al. 1972);* Reproductive and Developmental Toxicity observed **[CPSC 2011a]** DMEP meets the criteria for classification as toxic to reproduction and development **[ECHA 2011]** ME, derived by the metabolism of DMEP, may be the teratogenic agent (embryotoxic and fetotoxic); DMEP and metabolites are rapidly transferred to the fetus through the placenta **[Campbell, et al, 1984]**	Liver and kidney effects were observed **[Campbell, et al, 1984]**		Genotoxicity observed, dose-related trend *(NTP, 1993)* **[CPSC 2011a]**	
DnOP - Di-n-octyl phthalate - #117-84-0	C8	*Limited or inadequate evidence for reproductive/developmental toxicity* **[CPSC 2010a]** *No effect on AGD of male and female rat fetuses.* Incidence of supernumerary lumbar ribs was significantly elevated in all treated groups. *Results indicate low toxic potential for pregnant rats and did not affect intrauterine growth or embryonic/fetal survival. The limited adverse developmental effect in rats correlates with previous findings in mice.* LOAEL for developmental toxicity was 250 mg/kg/day **[Saillenfait 2011]** Showed significantly lower sperm counts/decreased motility at a 250 mg/kg/day dose level **[Kwack 2009]** Limited studies in animals show developmental effects at high doses; *Limited evidence of adverse effects, insufficient data for developmental toxicity; Some evidence of no adverse effect, negligible concern for reproductive toxicity; Reproductive toxicity NOAEL in mice = 7,500 mg/kg bw/day* and in rats is 350 mg/kg bw/day; Insufficient information for humans with regard to developmental toxicity and that *it is not likely to affect the human reproductive system;* It was noted that studies older than 2002 may not have looked for certain sensitive effects (e.g., anogenital distance), observed multiple generations, or exposed animals during the most sensitive periods of fetal development. **[NTP-CERHR 2003a]**	Hepatic structural and functional deficits have been observed in a variety of strains of both rats and mice. Structural alterations such as increased liver weights, centrilobular fat deposition and ultrastructural changes at the cellular level have been reported. Peroxisomal proliferation has been reported in Wistar but not Sprague-Dawley rats. Sufficient animal evidence, "Probable hepatotoxicant" **[CPSC 2010a]**	*No estrogenic effects* **[NTP-CERHR 2003a]** Structural and functional deficits have been observed both in rats and in vitro. Structural alterations such as reduced thyroid follicle size and decreased colloid density were reported, as were alterations in thyroid hormones T3 and T4. Sufficient animal evidence, "Probable thyroid toxicant" **[CPSC 2010a]**	Significantly increased kidney weights; dose-dependent changes in kidney ultrastructure have been reported in albino rat kidney glomeruli (atrophy, cellularity), proximal tubules (swelling, luminal obliteration, desquamation degeneration of epithelium), distal tubules (dilation, hyaline casts), vasa recta (edema), and interstitium (lymphocytic infiltration) following subchronic intraperitoneal exposures to 100, 300, and 600 mg/kg-day *(Khanna et al., 1990)* Sufficient animal evidence, "Probable renal toxicant" **[CPSC 2010a]**	

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DINP - Diisononyl phthalate - #28553-12-0; 68515-48-0	C8-C9 (some refs show range of C6-C10, with C6 and C7 backbone lengths)	Prenatal DINP exposure is associated with various malformations in offspring, while perinatal exposure leads to reproductive malformations in male pups; *Limited or inadequate evidence for reproductive toxicity*; May act in a dose-additive fashion to induce male reproductive effects following perinatal exposure; Sufficient evidence, "Probable developmental toxicant" **[CPSC 2010g]** Reduced maternal weight GD 20, PND 2 and 14 at 11,400 ppm. Reduced Pup weight PND 2 and 14 at 11,400 and 3,800 ppm; Induced MNGs (3,800 ppm) and LCAs (11,400 ppm) on PND 2, and reduced AGD (11,400 ppm) on PND 14; *Did not cause alterations in AGD, nipple retention or reproductive tract malformations in offspring observed on PND 49* **[Clewell 2013]** Testosterone concentration in the fetal testes was reduced at 250 and 750 mg/kg/day; Multinucleated germ cells were increased in the testes of rats at 250 and 750 mg/kg/day; The NOEL for this study was 50 mg/kg/day based on increased MNGs and reduced testes testosterone concentration in the fetal rat; Testes histopathology observed MNGs, *but no structural abnormalities* **[Clewell 2013a]** 2.3-fold less potent than DEHP in reducing fetal testicular testosterone production; Less potent than DEHP at reducing StAR and Cyp11a gene expression levels; DINP quantitatively different than other phthalates such as DEHP but not qualitatively different **[Hannas 2011]** Nipple retention, reduced anogenital distance, reduced sperm motility, and *increased sperm count in male offspring. Improved spatial learning in female offspring* **[Boberg 2011]** *No down-regulation of steroidogenesis on ED 19.5; No change in testicular and adrenal StAR P450scc, 3_HSD, or androgen receptor on ED 19.5* **[Adamsson 2009]** *No changes were exhibited in basal progesterone production after treatment;* An inhibitory action on oestradiol production by porcine granulosa cells was observed after the treatment **[Mlynarcikova 2007]** Seminal vesicles weights were significantly decreased by DINP at > 20 mg/kg bw/d; In addition LABC weights were decreased by DINP at 500 mg/kg bw/d **[Lee and Koo 2007]** Increase in hypothalamic grn and p130 in males and females on PND7; Decreased copulatory behavior in male rats; Lordosis quotient decreased in female rats; *LH, FSH, estrous cycles not affected* **[Lee 2006]** DINP at 20,000 ppm down-regulated PR in females **[Takagi 2005]** Treatment with DINP at 20,000 ppm resulted in degeneration of meiotic spermatocytes and Sertoli cells in the testis and decrease of corpora lutea in the ovary at week 11, *although changes remained minimal or slight* **[Masutomi 2003]** DEHP and DINP both reduced testicular testosterone ex vivo; reduced testosterone levels in testes and plasma of male fetuses GD21. Elevated plasma LH levels in male fetuses were observed. Tendency toward accumulating effects of DEHP and DINP on suppression of testosterone synthesis was observed **[Borch 2004]** *Maternal toxicity or reduced litter size were not seen;* Reduced pregnancy weight gain to GD21; Males displayed female-like areolas/nipples as infants 7.7% of males with reproductive malformations; *DINP order of magnitude less active than DEHP* **[Gray 2000]**	Exposure causes hepatocellular tumors in rats and mice. The tumors are believed to result from peroxisome proliferation, which does not occur significantly in humans. Sufficient evidence, "Probable hepatotoxicant" **[CPSC 2010g]** Liver weights, peroxisomal volume, and peroxisomal enzyme activity significantly elevated in both male and female mice at the tumorigenic levels; Cell proliferation elevated in male and female mice at 4,000 ppm and above; Apoptosis was elevated at the 4,000 and 8,000 ppm levels, paralleling the increases in liver weight; IARC criteria satisfied that peroxisomal proliferation was the mode of action for DINP-induced liver tumor induction in mice **[Kaufmann 2002]** Liver and kidney weights were elevated at Dietary level (%)s above ~ 110 mg/kg/day, consistent with evidence from other studies of peroxisomal proliferation at these levels **[Waterman 2000]** Recent report by the European Chemicals Agency also commented on evidence of multiple pathways for liver carcinogenesis, which could change the relevance of rodent study results to humans **[ECHA 2013]**	The results demonstrated that perinatal dietary exposure to EDCs for a limited period causes endocrine disruption in offspring at only high doses **[Masutomi 2003]** See also **Lee & Koo 2007** re: seminal vesicle and ventral prostate weights under DIDP. Seminal vesicle weights were significantly decreased by DINP at >20 mg/kg bw/d. DINP enhanced iodide uptake in a rat thyroid cell line (FRTL-5) at concentrations of 0.1 - 1 mM but not at lower concentrations **[Wenzel 2005, ECHA 2013]** *No effect on transcriptional activity of sodium/iodide symporter (NIS) observed* **[Breous 2005]**	California recommended addition of DINP to the Proposition 65 list as a carcinogen on December 5, 2013, based on evidence of other carcinogenic mechanisms of action in addition to activation of PPAR-alpha, and study findings inconsistent with the PPAR-alpha hypothesis. **[OEHHA 2013]** *Genotoxicity -> Negative* **[McKee 2000]** In chronic dietary studies, DINP treatment was associated with increased incidences of hepatocellular tumors in rats and mice of both sexes, renal tubular cell carcinoma in male rats, and mononuclear cell leukemia in Fischer 344 rats. The hepatocellular tumors are believed to arise by a mechanism (peroxisome proliferation and related effects) that is not easily induced in humans. The renal tubule tumors are believed to arise by a mechanism (alpha-2u-globulin) that is unique to male rats. The MNCL is a neoplasm with a high spontaneous rate in Fischer 344 rats that is considered of questionable relevance to humans. Limited animal evidence, "Possible" carcinogen **[CPSC 2010g]** Increased kidney weights and blood urea nitrogen levels in rats; Increases in mineralization of renal papillae and pigmentation of tubular cells were found in male rats; Kidney tumors in rodents; Sufficient evidence, "Probable" kidney toxicant **[CPSC 2010g]**	The available biological monitoring data suggest that infants/children are exposed to higher levels of phthalates than adults **[Saravanabhavan & Murray 2012]** Mixtures of phthalate esters with one another and with other anti-androgenic compounds exhibit cumulative, largely dose additive effects on male reproductive tract development when administered during sexual differentiation in utero. Since phthalate ester metabolites are detected in maternal and fetal body fluids, and androgen-signaling and insl3 are highly conserved among mammals, phthalates may potentially affect human reproductive development The secondary oxidized metabolites are the main metabolites and have longer half-lives than simple monoesters; therefore they may reside longer in the body **[Wittassek and Angerer 2007]**

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Phthalate Ester	**Carbon Chain length range**	**Reproductive/Developmental =** Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in offspring *(UN GHS 2003)* [OSHA 2015].	**Liver**	**Endocrine**	**Other**	**Comments**
		No changes in classic reproductive parameters, i.e. mating, male or female fertility, fecundity, gestational index, or length of gestation in either study; NOAELs for these effects were the highest Dietary Level (%)s tested, 500 mg/kg/day in the two-generation study and 1,000 mg/kg/day in the one-generation study. *No testicular effects in parental animals exposed as juveniles and young adults at 960 mg/kg/day in the one-generation study.* *In the two-generation study, no testicular effects in either the P1 males, exposed as juveniles and young adults or the P2 (F1) offspring exposed in utero, through lactation, and continuously to terminal sacrifice.* The NOAEL was 470 mg/kg/day. Offspring survival was reduced at the 1.5% level (~1,100 mg/kg/day) but unaffected at the 1% level (~760 mg/kg/day). Decreased offspring body weights both at postnatal day (PND) 0 and during lactation; however, the PND 0 effects were only clearly related to treatment at the 1.5% level. Weights of offspring during lactation were significantly reduced but within the historical control range at Dietary Level (%)s below 1%. *Adult survival was unaffected at any level in either study,* but weight gain was significantly reduced at the 1% level (~600 mg/kg/day); *Shows no gross reproductive effects in a two generation study* **[Waterman 2000]** Minimal concern for reproductive or developmental toxicity **[NTP-CERHR 2003c]**				
Din911P - 1,2-Benzenedicarboxylic acid, 1-nonyl 2-undecyl ester, branched and linear - #111381-91-0	C8-C11	*No signs of maternal toxicity, as assessed by adjusted maternal body weight gain throughout gestation and clinical examinations, and no effects upon litter size, fetal survival or body weight;* Pups of the high dose D79P and intermediate and high dose D911P groups showed increased incidences of supernumerary lumbar ribs; There was a significant increase in dilated renal pelves in pups of the low dose D79P and high dose D911P groups, but only for D911P was there a significant trend; *The NOAEL for maternal toxicity for both D79P and D911P is 1,000 mg/kg/day;* The NOAEL for values for developmental toxicity are 500 mg/kg/day D79P and 250 mg/kg/day D911P **[Fulcher 2001]** Both D79P and D911P markedly reduced body weight gain in F0 and F1 adult males at the highest dose, but females were affected to a lesser extent. *There was no impairment of fertility, fecundity, or development in either generation,* but body weights of offspring in the 1.0% D79P and 1.0% D911P groups were slightly and transiently reduced over the weaning period. Although decreases in the weight of several organs were accounted for by depressed body weight, ovary weights were reduced in both generations exposed to 1.0% D79P, and epididymidal weights were slightly reduced in adults of both generations exposed to 1.0% D911P. *However, ovarian function—assessed by the oestrus cycle and mating behaviour—and epididymidal sperm concentration, motility, and morphology were unaffected by either substance.* Treatment resulted in liver changes, particularly in males, characterised by increased liver weight in young animals, histopathologic changes and reduced organ weight in mature animals, and an increase in palmitoyl CoA oxidase activity. *In conclusion, neither D79P nor D911P impaired reproductive function in rats when administered in the diet at levels that induce systemic toxicity,* and the NOAEL for effects on reproduction in the rat is 0.5% for both D79P and D911P. **[Willoughby 2000]**	See developmental toxicity notes **[Willoughby 2000]** In the systemic studies, some liver effects were noted, but considered not of toxicological significance *(Brown et al., 1970)* **[CPSC 2010b]**		*Acute toxicity -> greater than 20,000 mg/kg (Brown et al., 1970)* **[CPSC 2010b]**	

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DIDP - Diisodecyl phthalate - #26761-40-0; 68515-49-1	C8-C10	"Probable" reproductive (based on Hushka 2001 - see below) and developmental toxicant (Increased incidences of minor skeletal variations; Offspring survival was affected and decreased pup body weight was observed at 0.2 and 0.4% DIDP in the F1 and F2 generations - based on Hushka 2001 - see below); Probable toxicant in humans by oral route based on sufficient evidence of reproductive and developmental effects in animals **[CPSC 2010f]** *No significant change in sperm count,* however reduced sperm motility **[Kwack 2009]** *No effects on fertility were observed; No effects on live birth index were observed*, but reduced offspring survival was observed at postnatal days 1 to 4. This reduced survival was more pronounced in the F2 generation in which statistical significance was achieved at levels of 0.2% DIDP and greater; *There were no notable alterations in developmental landmarks;* Increase in age at vaginal opening of F1 generation females; relative testes, epididymis and seminal vesicle weight increase vs. controls in F1 males without histological changes; Decrease in normal sperm in all treated groups; NOAELs of 0.06% (~50 mg/kg/day) for F2 offspring survival and 0.8% (~ 600 mg/kg/day) for fertility, other measures of reproductive function, and developmental landmarks **[Hushka 2001]** The present study shows that diisodecyl phthalate (DIDP), significantly enhanced iodide uptake when concentrations in the magnitude between 10^{-4}M and 10^{-3}M were applied. Specific inhibition of NIS demonstrated that enhancement of iodide uptake is due to NIS. DIDP seems to enhance iodide uptake in thyroid as a consequence of sodium/iodide symporter transcriptional activation. The demonstrated stimulation is not very strong, but the accumulation of phthalates may contribute to thyroid hyperfunction. **[Wenzel 2005]**	Liver effects included increased liver weight, increased peroxisomal enzyme levels and histopathologic changes (swelling and vacuolization of hepatocytes); Increase in kidney weight observed; Probable toxicant in humans by oral route based on sufficient evidence of systemic (liver, kidney) **[CPSC 2010f]** Small mammalian study of beagles (Hazelton 1968) shows a dose related increase in liver weights **[NTP-CERHR 2003b]** Non-neoplastic changes observed in the liver (parenchymal inflammation, fatty changes, diffuse hepatocyte hypertrophy with eosinophilic granules and focal necrosis) and kidneys (tubular basophilia and tubular hyperplasia) in rasH2 and wild-type mice; Neoplastic lesions had a higher number of hepatocellular adenomas in the male rasH2 mice receiving 1% DIDP, compared with the findings in the liver of control rasH2 mice or wild-type mice; Incidence of hepatocellular adenomas in the 0.1, 0.33, and 1% DIDP exposed rasH2 mice was 7% (1/15), 7% (1/15), and 33% (5/15), respectively **[Cho 2011]** Significant decreases in overall survival and body weights, and increases in the relative weights of kidneys and liver were noted in both sexes of the highest dose groups; *No treatment-related neoplastic lesions were observed in the internal organs* ; DIDP failed to maintain the catalase-inducing potential between early and late expressions of catalase protein from western blotting, immunohistochemistry and enzyme activity measurements; These results suggest that the non-carcinogenicity of DIDP in F344 rats was due to its limited potential for peroxisomal proliferating activity **[Cho 2008]** Decreases in adult body weight along with corresponding increases in liver and kidney weights and histopathologic changes indicative of peroxisomal proliferation were observed **[Hushka 2001]**	Seminal vesicles weights were significantly decreased by **DIDP** at 500 mg/kg bw/d. Ventral prostate weights were significantly decreased in animals treated with 500 mg/kg bw/d **DIDP.** These data suggest that some phthalates possess antiandrogenic activity, and that multiple cross-talk between androgen, estrogen, and steroid hormone receptors occurs. Anti-androgenic effects were observed. **[Lee and Koo 2007]** See thyroid notes in reproductive/development al **[Wenzel 2005]**	*Not considered to be carcinogenic to humans (based on assumption of liver peroxisome proliferation as MOA, and not relevant to humans)* **[CPSC 2010f]** Concerns regarding multiple pathways for carcinogenicity **[ECHA 2013 and OEHHA 2013]** *Genotoxicity -> Negative* **[McKee 2000]**	The available biological monitoring data suggest that infants/children are exposed to higher levels of phthalates than adults; DIDP breaks down to carboxylic acid by oxidation, it does not metabolize to shorter side chain monoesters **[Saravanabhavan & Murray 2012]** The secondary oxidized metabolites are the main metabolites and have longer half-lives than simple monoesters; therefore they may reside longer in the body **[Wittassek and Angerer 2007]**
DPHP - Di-2-propyl heptyl phthalate - #53306-54-0	C7, C10	Significant reduction in sperm velocity indices, reversible after 4 wk recovery. *No other significant effect on sperm (UCC 1997)* . **[CPSC 2010h]** Significant maternal toxicity at high dose (insuffic. care of fur; GD 6-10 reduced food consumption and reduced body wt gain; GD 6-8 loss of body wt; accum. of fluid in uterus, increased postimplantation loss, 2.2% dams with only resorptions in uterus. No teratogenicity observed; high dose fetuses had increased soft tissue variations *(BASF 2003)* . **[CPSC 2010h]** Insufficient amount of animal data and poorly described methodologies resulted in conclusion of "insufficient evidence" for designation of DPHP as a reproductive toxicant under CPSC criteria. **[CPSC 2010h]** *No effects on fertility or repro performance (Greenscreen assessment Repro score Low) (BASF 2009)* **[GC3 2012]** Developmental effects only in high dose group (Devel. score Low) *(BASF 2003)* **[GC3 2012]**	Increased liver wt at all doses ≥ 40 mg/kg/day and dose-related adrenal effects (vacuolization of the zona glomerulosa) in both sexes and at all doses ≥40 *(UCC 1997),* supporting conclusion that DPHP is a subchronic toxicant. However, lack of supporting studies resulted in conclusion of "inadequate evidence" for designation of DPHP as a chronic hazard under CPSC criteria. **[CPSC 2010h]**	Draft Greenscreen assessment assigned endocrine activity score of Moderate based on unpublished BASF study: increased basophilic cells in anterior pituitary, inc. hypertrophy of follicular epithelium in thyroid, hepatocellular hypertrophy and induction of enzymes associated with peroxisome proliferation (PP). Noted that thyroid effects unlikely due to PP. **[GC3 2012]**		"Currently, DPHP metabolites cannot be distinguished from the metabolites of DIDP." **[CPSC 2014]** The secondary oxidized metabolites are the main metabolites and have longer half-lives than simple monoesters; therefore they may reside longer in the body **[Wittassek and Angerer 2007]**
DUP or DUDP - Diundecyl phthalate - #3648-20-2	C10-C11	Decrements in testicular weight, sperm count and motility; Limited animal evidence for reproductive and developmental toxicity **[CPSC 2010c]** *The number of live fetuses, percent of post-implantation loss and of resorptions, fetal sex, and fetal body weights were not affected. No evidence of teratogenicity;* Small decreases in AGD of male fetuses were noted at 0.5 and 1 g DUDP/kg/day; The incidence of fetuses with supernumerary lumbar ribs was significantly higher than controls (this effect is considered reversible) at 0.5 and 1 g DUDP/kg/day **[Saillenfait 2013]** Significantly decreased sperm numbers and sperm motility **[Kwack 2009]**	Increases in relative liver weight, histopathology, and liver enzymes; Sufficient animal evidence for hepatotoxicity **[CPSC 2010c]**			

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DIUP - Diundecyl phthalate, branched and linear - #85507-79-5	C9-C11				*Genotoxicity -> Negative* **[CPSC 2010d]** Repeated dose toxicity evidence of peroxisomal proliferation *(ECB 2000)* **[CPSC 2010d]**	DHinUP (C7-11 branched and linear) on SVHC Candidate List. This DIUP CAS# included Palatinol 711P.
DTDP - Ditridecyl phthalate - #119-06-2	C10-C13	Reproductive effects in a Japanese study were shown at higher doses *(CIPC 2010 b,c); Inadequate evidence for reproductive/developmental toxicity* **[CPSC 2010e]** *The # of live fetuses, % of post-implantation loss and of resorptions, fetal sex, and fetal body weights were not affected. There was no evidence of teratogenicity.* [*Not developmentally toxic up to 1,000 mg/kg/day]* **[Saillenfait 2013]**	Limited animal evidence of hepatotoxicity - hepatocellular hypertrophy and increased liver weight in both sexes **[CPSC 2010e]**	*Inconsistent results - one sample was weakly estrogenic; another from different source was inactive; BPA confounding concern (Harris et al. 1997)* **[CPSC 2010e]** Small thymus effects in all dose groups – although not statistically significant or dose related (CIPC 2010) **[CPSC 2010e]**	Limited animal evidence of renal toxicity - Kidney (eosinophilic bodies in renal tubular cells and increased kidney weight in males) following 6-week gavage administration; Few observations of mild hyperplasia in the renal pelvis epithelium and urinary bladder transitional epithelium in female rats **[CPSC 2010e]**	CPSC didn't calculate ADI [Acceptable daily intake is defined as the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers] and included limited studies **[CPSC 2010e]**