

Propyl paraben	(CAS 94-13-3)
Butyl paraben	(CAS 94-26-8)
Methyl paraben	(CAS 99-76-3)
Ethyl paraben	(CAS 120-47-8)
<i>para</i> -Hydroxybenzoic acid	(CAS 99-96-7)

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Due to similarities in use, exposure, and toxicity; the parabens are grouped in one summary.

### Summary

These five chemicals meet the Department of Ecology's criteria for inclusion on the CHCC list. There is widespread exposure to parabens and p-hydroxybenzoic acid (PHBA) in the U.S., and because of evidence of endocrine disruption, it is important to collect more information about the use of these chemicals in children's products. Although there were both positive and negative studies for many potentially harmful effects, the weight of evidence indicates that these chemicals have estrogenic activity, can interfere with normal sperm development, and can alter testosterone levels. Several parties contend that parabens are safe at the levels used in products, but there is some debate about the margin of safety. While toxicity studies have focused on the effects of individual compounds, children's products often contain mixtures of two or more parabens. The parabens and p-hydroxybenzoic acid are structurally related compounds that often appear to have similar biological activities in experimental studies, and it is therefore important to consider the potential for additive or synergistic effects from exposure to mixtures of these chemicals.

### Toxicity

All five chemicals have been classified as Category 1 endocrine disruptors by the European Union.<sup>1</sup>

Estrogenic effects: All the widely used parabens have been shown to possess estrogenic activity to different extents in different assay systems *in vitro* and *in vivo*. Twenty four out of twenty five *in vitro* studies of estrogenic effects reported positive findings for parabens.<sup>2</sup> The estrogenic effects of treatment with multiple parabens appear to be additive.<sup>3</sup> The estrogenic activity of parabens is known to increase with increasing chain length and with branching of the alkyl chain. Estrogenic activity of PHBA has been demonstrated in several assays.<sup>2</sup>

In uterotrophic assays, all four parabens and PHBA showed estrogenic activity in at least one *in vivo* study, while at least one other study showed negative results for each compound.<sup>2</sup> The lowest NOAELS and LOAELS are shown in the Table 1 below.<sup>2</sup>

Table 1

Compound	NOAEL (mg/kg bw)	LOAEL (mg/kg bw)
Methyl paraben	5.5	16.5
Ethyl paraben	6	18
Propyl paraben	6.5	20
Butyl paraben	0.7	7
PHBA	0.5	5

Parabens generally have lower binding affinity to estrogen receptors than some other estrogenic ligands (such as 17 $\beta$ -estradiol or DES), and parabens are often termed “weak estrogens”. The estrogenic potentials of parabens have been studied in estrogen receptor (ER)  $\alpha$  competitive binding assays, as well as studies that examined other aspects of estrogenicity including ligand ability to regulate an estrogen-responsive gene (ERE-CAT) transfected into MCF-7 cells, and ligand ability to regulate estrogen-dependent proliferation of MCF-7 cells. In the competitive binding assay, all parabens studied were at least 10,000 to 100,000 times less potent than 17 $\beta$ -estradiol.<sup>4</sup> In MCF-7 cells with a stably transfected estrogen-regulated ERE-CAT reporter gene, the tested parabens showed effects similar to 17 $\beta$ -estradiol, although at 1000–10,000 times greater concentrations. Depending on the endpoint measured and the specific paraben under study, these compounds are from 1000 to 1,000,000 times less potent than 17 $\beta$ -estradiol.<sup>4</sup>

However, with sufficient concentrations, the parabens gave responses in whole cell assays in terms of increased gene expression and cell proliferation in human breast cancer cells of the same magnitude as 17 $\alpha$ -estradiol. This shows that parabens are not partial agonists, as might be implied by the term ‘weak’, but give full agonist responses in whole cells at sufficiently high concentrations. There is some indication that blood levels of parabens and their metabolites are significantly higher than levels of natural estradiol and therefore, despite their lower binding affinity, could interfere with normal functioning of processes regulated by estrogens.<sup>2</sup>

Effects on males: Studies in young male rats have shown adverse effects on sperm production and testosterone levels following oral exposure to parabens with longer side chains, specifically butyl paraben and propyl paraben.

Propyl paraben (8 weeks of dietary exposure) reduced daily sperm production at all doses tested (10 mg/kg, 100 mg/kg, and 1000 mg/kg). Similarly, serum testosterone levels were reduced at all three dose levels, but the effect was statistically significant only at 1000 mg/kg.<sup>5</sup>

Butyl paraben reduced daily sperm production (testis sperm counts) as well as epididymal cauda sperm counts in a dose-related manner in all applied doses of approximately 10, 100 and 1000 mg/kg bw/day. Serum testosterone was reduced at 100 and 1000 mg/kg bw/day showing a dose-response relationship. Relative epididymis weight was reduced at 100 and 1000 mg/kg bw/day with a dose-response

relationship.<sup>6,7</sup> These results suggest a LOAEL of 10 mg/kg bw/day and no identifiable NOAEL for propyl paraben and butyl paraben.

Hoberman et al.<sup>8</sup> performed a repeat of the 2001 study by Oishi<sup>6</sup> by exposing young male rats in the diet to 10, 100 and 1000 mg/kg bw/day of butylparaben. This study was performed under Good Laboratory Practices conditions and included a higher number of animals than the Oishi study. The authors reported “no adverse effects” at all dose levels concluding a NOAEL of 1000 mg/kg bw/day. However, serum testosterone was reduced significantly after 3 weeks of dosing at 100 and 1000 mg/kg bw/day.

In a study of methyl paraben, Hoberman et al. reported statistically significant increases in the number of abnormal sperm in the two highest dose groups (100 mg/kg and 1000 mg/kg), and the testicular spermatid concentration appeared dose-dependently decreased (to 77% of control level), although this was not statistically significant.<sup>8</sup>

Recent reports have documented that several parabens have the ability to bind to the androgen receptor and anti-androgenic activity was found for all the parabens tested. Additionally, in a recent *in vitro* study, methyl-, propyl- and butyl-4-hydroxybenzoate were shown to be androgen receptor antagonists, and some of the parabens could inhibit testosterone induced transcriptional activity by as much as 40% at a concentration of 10µM.<sup>9</sup>

## **Exposure**

Parabens are the most widely used preservatives in cosmetic products.<sup>10</sup> Various parabens and paraben mixtures are intentionally added to thousands of cosmetic products. Methyl paraben and propyl paraben have been Generally Recognized As Safe by the FDA for direct addition to foods at levels <0.1%. Para-hydroxybenzoic (PHBA) acid is a precursor used in the manufacture of parabens and is also a common metabolite in humans following oral or dermal exposure to parabens.

Parabens are used in many children's products.

The Danish EPA identified methyl paraben as a listed ingredient in 95 of 208 children's personal care products, 7 of 28 sunscreens, and 7 of 32 lotions in studies of cosmetics marketed for children.<sup>11,12</sup> Methyl paraben was also found in 2 of 26 marker pen sets,<sup>13</sup> 1 of 3 gel pens,<sup>13</sup> and several slime toys.<sup>14,15</sup> A Dutch study of plastics in children's products found methyl paraben in 1 out of 18 samples of ethylene vinyl acetate plastic.<sup>16</sup>

The Danish EPA identified ethyl paraben as a listed ingredient in 46 of 208 children's personal care products, 2 of 28 sunscreens, and 4 of 32 lotions in studies of cosmetics marketed for children.<sup>11,12</sup> Ethyl paraben was found in 1 of 14 slime toys.<sup>14</sup>

The Danish EPA identified propyl paraben as a listed ingredient in 70 of 208 children's personal care products, 5 of 28 sunscreens, and 6 of 32 lotions in studies of cosmetics marketed for children.<sup>11,12</sup> Propyl paraben was found in 3 of 14 slime toys.<sup>14</sup>

The Danish EPA identified butyl paraben as a listed ingredient in 48 of 208 children's personal care products, 1 of 28 sunscreens, and 1 of 32 lotions in studies of cosmetics marketed for children.<sup>11,12</sup> Butyl paraben was found in 1 of 14 slime toys.<sup>14</sup>

The Danish EPA found para-hydroxybenzoic acid in 1 slime toy.<sup>15</sup> A Dutch study of plastics in children's products found para-hydroxybenzoic acid in 2 out of 18 samples of ethylene vinyl acetate plastic.<sup>16</sup>

Analysis for parabens in urine of the general U.S. population was conducted in the NHANES survey during 2005 – 2006; and two or more were detected in almost all people sampled.<sup>17</sup> Table 2 below shows percent detection for four parabens.

Table 2

Compound	Percentage detected
Methyl paraben	99.1%
Ethyl paraben	42.4%
Propyl paraben	92.7%
Butyl paraben	47.0%

For some children 6 to 11 years old, urinary excretion exceeded one milligram per day (Table 3).<sup>17</sup>

Table 3

Compound	Urinary Excretion 50 <sup>th</sup> percentile (µg/L)	Urinary Excretion 95th percentile (µg/L)
Methyl paraben	25	1560
Ethyl paraben	Not detected	9.9
Propyl paraben	2.5	125
Butyl paraben	Not detected	7.5

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