

“Parabenoia” Debunked, or “Who’s Afraid of Parabens?”

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Parabens have been used as preservatives in foods, injectables, and topical preparations for nearly 10 decades. Present in nature, rapidly metabolized by skin and liver enzymes, they have an excellent safety record. However, in the past 15 years, they have been under scrutiny for their alleged estrogenic and antiandrogenic effects, as well as their putative role in promoting cancerogenesis through endocrine disruption. Scientific articles supporting these assertions have led the European Community to ban or restrict the use of some parabens. Despite that methylparaben and ethylparaben have negligible endocrine disruption activity, the food, pharmaceutical, and cosmetic industries are under pressure from scare campaigns in the media and are responding by replacing parabens with other biocides that cause multiple cases, and even worldwide epidemics, of allergic contact sensitization. In the present review, we present a balanced account of the published literature about the metabolism and potential toxicology of parabens.

Introduced in the 1920s, the esters of parahydroxybenzoic acid, or parabens, are the most widely used biocides in foods and cosmetics. These antimicrobial compounds are naturally present in living organisms and plants such as strawberries, blueberries, grapes, olives, yeast, and barley.^{1,2} Nonmutagenic in the Ames test and deemed nontoxic, they are also inexpensive, odorless, and colorless.³ Four esters—methylparaben, ethylparaben, propylparaben, and butylparaben—are commonly used, most often in association with each other for increased effectiveness at low concentration.^{4,5} Isopropylparaben, isobutylparaben, phenylparaben, and benzylparaben are used less often. When applied to the skin, they are hydrolyzed to parahydroxybenzoic acid by keratinocyte carboxylesterases, whereas ingested parabens are metabolized by intestinal and hepatic esterases.

Poul Bonnevie is credited with the first description of allergic contact dermatitis from ethylparaben in a fungicidal cream.⁶ In the subsequent decades, additional reports confirmed the sensitizing potential of parabens. The cosmetic and pharmaceutical industries reacted by introducing new biocides, such as the formaldehyde releasers and, more recently, the isothiazolinones. From a contact dermatitis point of view, parabens have a much better record than all of the other families of cosmetic preservatives. Their rate of contact sensitization has remained constantly low for decades, in the range of 0.5% to 3.5%, but mostly

around 1%, of all patients who attend a contact dermatitis clinic.^{3,7–9} For the past 12 years, the North American Contact Dermatitis Group has reported sensitization rates for the paraben mix to fall between 0.6% and 1.4%.¹⁰ Most cases of sensitization occur when paraben-containing products, such as emollients and corticosteroid creams, are applied to eczematous or ulcerated skin with a defective epidermal barrier. In fact, patients thus sensitized are often able to tolerate paraben-containing products applied to normal skin, an effect known as the “paraben paradox.”³

NEW CONCERNS AND REGULATORY CONTROLS

In the past 20 years, the safety of parabens has been challenged. Because of their weak estrogenic activity, they are now suspected to be potential endocrine disruptors that may contribute to the development of breast cancer and the occurrence of male infertility. The alarmist tone of some scientific publications has had thunderous echoes in the media, feeding the delusions of “chemophobes” who see evil in any product that does not come from a “natural” source. A respected Canadian environmental protection organization, the David Suzuki Foundation, has parabens on its list of “Dirty Dozen” cosmetic chemicals to avoid. Ever sensitive to the demands of its customers, the cosmetic industry is now marketing entire lines of paraben-free products. Given that the biocides that are replacing the parabens are more allergenic, the current worldwide epidemic of allergic contact dermatitis from methylisothiazolinone comes as no surprise.^{11,12}

In cosmetic products, according to the EU Council Directive of 2000, parabens are allowed at a concentration of 0.4% for a single paraben and 0.8% for mixtures of parabens.¹³ In March 2011, however, Denmark banned the use of propylparaben and butylparaben in cosmetic products for children younger than 3 years. This led the EU Scientific Committee on Consumer Safety

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DOI: 10.1097/DER.0000000000000147

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to reevaluate the subject and suggest that allowed concentrations remain unchanged for methylparaben and ethylparaben but that the sum of individual concentrations of propylparaben and butylparaben in finished products be limited to 0.19%.¹⁴ On the basis of this report, the EU Commission amended the Directive and, in 2014, banned isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben. As of April 16, 2015, the limit of 0.19% for propylparaben and butylparaben applied, and the use of these 2 preservatives is now prohibited in leave-on cosmetic products designed for application on the diaper area of children younger than 3 years. No regulation exists in the United States and Canada, and manufacturers are under no obligation to follow the guidelines of the US Cosmetic Ingredient Review Expert Panel or Health Canada that recommends the same measures as legislated in the EU.¹⁵

ESTROGENIC ACTIVITY OF PARABENS

In 1998, Routledge et al¹⁶ showed that parabens possessed estrogenic activity when assessed in vitro: these esters could bind to rodent uterine estrogen receptor and increase estrogen-regulated gene expression in yeast cells. In this assay, butylparaben was the most estrogenic, being 10,000-fold less potent than 17 β -estradiol. Estrogenic activity augments with increasing length of the alkyl side chain, so that among members of this family, methylparaben is the least estrogenic, and n-butylparaben is the most estrogenic. In an in vivo assay that measured the weight of immature rat uterus, oral administration of various parabens was without effect. However, subcutaneous administration of high doses (400-mg/kg body weight) of butylparaben increased uterine weight, an effect approximately 100,000 times less potent than 17 β -estradiol.¹⁶ Hossaini et al¹⁷ investigated the estrogenic activity of parahydroxybenzoic acid and its various esters administered orally and subcutaneously in a mouse and rat uterotrophic assay. Oral administration was without effect, and butylparaben was the only compound to produce a weak effect when administered subcutaneously in doses of 600-mg/kg body weight per day.¹⁷

In 2002, Byford et al,¹⁸ members of the research group directed by Philippa Darbre at the University of Reading, United Kingdom, proved that methylparaben, ethylparaben, propylparaben, and n-butylparaben can bind to cytosolic estrogen receptor, increase estrogen-regulated gene expression, and increase cell growth in the MCF7 estrogen-sensitive human breast cancer cell line. Subsequent publications demonstrated similar, albeit slightly higher, estrogenic activity of isobutylparaben¹⁹ and benzylparaben.²⁰ In the latter study, the authors observed increased uterine weight in the immature mouse assay after topical application of 3 daily doses of 33 mg (equivalent to a dose of 20-mg/kg body weight).²⁰

In 2001, in the European Journal of Cancer Prevention, Darbre²¹ published an article with the alarming title: "Underarm Cosmetics are a Cause of Breast Cancer." In this article, she exposed her hypothesis that the rising incidence of breast cancer

could be secondary to environmental exposure of cancer-promoting agents in antiperspirants and deodorants. Her arguments were that (1) the rise in breast cancer incidence since the 1970s parallels the increased use of underarm deodorants and antiperspirants; (2) there is a disproportionately high incidence of breast cancer in the upper outer quadrant of the breast, close to the area where underarm cosmetics are applied; (3) breast cancer is more common in the left breast, possibly reflecting that most women are right handed and apply a larger amount of underarm cosmetics to the left axilla; (4) only 10% of breast cancers can be explained by genetic susceptibility, whereas 90% are due to other risk factors, particularly lifetime estrogen exposure; (5) parabens, and possibly other ingredients in underarm cosmetics, have demonstrated estrogenic activity; and (6) parabens, being lipophilic, may penetrate the skin "without even invoking any major physiological carrier such as blood or lymphatics" and accumulate in surrounding tissues, including fat and breast.²¹ It should be noted that the highest amount of breast tissue is found in the upper outer quadrant, which may explain the higher incidence of breast cancer in this area.²² Furthermore, the lymphatic circulation goes from the breast to the axilla and not in the opposite direction.

Since the publication of this seminal article, Darbre²³ has devoted her research to substantiate her assumptions.²² In 2004, she published in the Journal of Applied Toxicology another article entitled "Concentrations of Parabens in Human Breast Tumours."²⁴ Using high-pressure liquid chromatography followed by tandem mass spectrometry, her team was able to extract parabens from 18 of 20 samples of breast tumor material. Methylparaben accounted for 62% of the total amount of retrieved parabens. In the same issue of the journal, an accompanying editorial by Harvey and Everett²⁵ cautioned that the detection of parabens in breast tumor does not imply causality of the individual cancer and that further research was needed.

Nevertheless, harsh critics followed the publication of the Darbre et al article. Golden and Gandy,²⁶ Jeffrey and Williams,²⁷ and finally, Flower²⁸ pointed out some of the limitations of the study: (1) a small number of tumors were analyzed; (2) no information was provided about the background of the patients, location and type of the tumor (ie, estrogen receptor positivity status), use of cosmetics, and so forth; (3) absence of control tissue; and most importantly, (4) blanks (no tissue) were also positive for parabens, suggesting contamination during the analytical process. In her reply to Golden and Gandy, Darbre reiterated that the purpose of her study was to investigate whether parabens can be detected in breast tissue.²⁹ She reaffirmed that her study could not identify the source of these parabens and that it never claimed that the presence of parabens in malignant breast tissue was the cause of the neoplasm. Darbre tackled the issue of the presence of parabens in her blank samples by subtracting the amount found in blanks from that found in the analyzed tumors, thus her surprising findings of negative figures for some of her samples. On the other hand, it should be noted that authors of the letters to the editor,

criticizing the study, were consultants for the Cosmetic, Toiletry and Fragrance Association or The Cosmetic, Toiletry and Perfumery Association Ltd and may not have been completely free of bias themselves.

FURTHER EVIDENCE OF ESTROGENIC ACTIVITY

In 2008, Darbre and Harvey³⁰ published an extensive review of existing studies about the toxicology of parabens. The authors cite the results of multiple *in vitro* and *in vivo* studies that assessed the estrogenic activity of parabens. Of 25 *in vitro* studies (estrogen receptor-binding assays), only one showed negative results. Of the 30 *in vivo* studies (rat or mouse uterotrophic assays), 7 were negative. Although the majority of studies showed positive results, for methylparaben and ethylparaben, 2 *in vivo* studies were positive,³¹ and 2 were negative.^{17,32} Furthermore, in recent years, parabens have been shown to exert their estrogenic activity not only by binding the estrogen receptor but also by inhibiting sulfotransferases, enzymes that inactivate estrogens.³³

In 2013, Charles and Darbre³⁴ published a more concerning study where they claimed that parabens at concentration found in human breast cancer cells were able to stimulate MCF-7 human breast cancer cells *in vitro*. They showed that 43 (27%) of 160 of their human breast tissue samples contained at least 1 paraben at concentration where they observed lowest observed effect concentrations for MCF-7 proliferation. They also showed that combined exposure to all 5 parabens at the same concentrations showed a significant increase in proliferation of MCF-7 cells. This *in vitro* study focused on proliferation of already-established breast cancer cells but did not address the potential for malignant transformation from a benign state. To date, no human studies have showed convincing evidence that parabens cause and stimulate breast cancer.

EPIDEMIOLOGICAL STUDIES

Two epidemiological studies that addressed the abovementioned issue came up with conflicting results. Being retrospective, these studies have their own limitations. Mirick et al³⁵ published the first study in 2002 in the *Journal of the National Cancer Institute*. It was a population-based, case-controlled study that included 813 patients diagnosed with breast cancer and 793 control subjects. Participants were questioned about use of antiperspirants and deodorants or application of such products within 1 hour of shaving. The risk for breast cancer did not increase with any of those activities. One year later, McGrath³⁶ published in the *European Journal of Cancer Prevention* a study that stratified 437 surviving female patients with breast cancer into nonusers and minimum, middle, and maximum users of deodorants and antiperspirants. The mean age at the time of breast cancer diagnosis was progressively lower from the nonusage to maximum usage groups. In addition, beginning these activities before the age of 16 years was associated with a significantly earlier age at diagnosis.

An association between underarm cosmetics and breast cancer was postulated, and a call for further studies was made. Darbre quotes this study as corroborative evidence of her claims, although the authors did not target parabens, but aluminum salts as potential culprits. It should be noted that no epidemiological study specific to paraben and breast cancer development has ever been performed.

TRANSDERMAL PENETRATION

In their 2008 article, Darbre and Harvey³⁰ review the absorption and metabolism of parabens. They state that, regarding transdermal absorption, other investigators have now shown that (1) topical application of parabens to the skin can result in systemic absorption detectable in human urine,³⁷ (2) esters can enter the human body without degradation to parahydroxybenzoic acid by cutaneous esterases and possibly by intestinal and liver enzymes,³⁸ (3) methylparaben penetrates the skin to the greatest extent, and (4) repeated cutaneous application of a butylparaben-containing preparation causes a 6-fold accumulation of the preservative in the stratum corneum between 1 and 4 weeks.³⁹

The authors mention that not only underarm products but also cosmetics as a whole, including shampoos and moisturizers, need to be assessed for their potential to cause systemic absorption and possible tissue accumulation of parabens in the human body. They are concerned that repeated exposure for many years, especially in highly sensitive subgroups such as babies and children, could lead to endocrine disruption and play a role in the occurrence of breast cancer. They conclude their article with a call for additional research “to define clearly whether there are additive or even inhibitory effects in human breast cancer cells of combination of all the paraben esters and combinations of all the paraben esters together with other cosmetic estrogens and also environmental estrogens known to enter the breast through diet.”

One study by Frederiksen et al⁴⁰ determined the concentration of 5 parabens—methylparaben, ethylparaben, n-propylparaben, n-butylparaben, and benzylparaben—in urine, serum, and seminal plasma samples from 60 healthy Danish men. This study found only negligible urine, serum, and seminal plasma levels of n-butylparaben, with median values of 0.19, less than 0.33, and less than 0.06 ng/mL, respectively. Methylparaben and n-propylparaben were measurable in the majority of serum and seminal plasma samples, whereas the other parabens could only be detected in some. In all 3 matrices, significant correlations between the parabens were seen. Furthermore, urinary paraben concentrations correlated with the concentrations present in both serum and seminal plasma. These measured levels of parabens presumably reflect only a fraction of human exposure, as it is believed that most of the absorbed parabens are rapidly transformed into harmless and nonspecific metabolites. The fraction of the parent compounds excreted in urine may depend on the route of exposure. Compared with oral ingestion, uptake of parabens through the skin may thus result in higher serum and urine concentrations of the parent compounds because they bypass hepatic degradation. Nevertheless, the presence of parent compounds

in the 3 human compartments indicates that uptake of parabens results in exposure of human tissues to potentially harmful substances. However, another study conducted in 332 postmenopausal women failed to detect butylparaben and found traces of methylparaben, ethylparaben, and propylparaben (medians of 9.4, <3, or <2 ng/mL, respectively) in only a fraction of analyzed plasma samples.⁴¹

ANTIANDROGENIC AND REPRODUCTIVE EFFECTS

Parabens have been found to possess antiandrogenic activities, similar to phthalates and bisphenol A. In the Oishi^{42–44} studies, exposure of prepubertal male rats to propylparaben or butylparaben in the diet from weaning to adulthood at nominal dose levels of 10, 100, or 1000 mg/kg/d inhibited spermatozoon production after puberty. Testosterone levels were significantly decreased at the highest dosage, but because no data were available for luteinizing hormone or follicle-stimulating hormone, no conclusion could be drawn about whether the decrease in testosterone level was due to a central effect or a peripheral effect. Although direct testicular toxicity could not be ruled out, endocrine disruption was suspected to be the primary cause in light of previously described *in vitro* and *in vivo* data. In these studies, no data were presented on sperm recovery or plasma exposure, and the maximum nontoxic dose was not determined, so comparison with human exposure levels, if any, is impossible.

An attempt to reproduce these results failed: although the repeat study used the same protocol and rat strain and a larger number of animals and measured additional reproductive end points, it found no adverse reproductive effects at dietary dose levels of up to 10,000 ppm, corresponding to greater than 1000 mg/kg/d of methylparaben or butylparaben.⁴⁵ Interestingly, Oishi³² himself was unable to document any spermatotoxic effects with methylparaben and ethylparaben.

In another recent study focusing on a highly sensitive end point of estrogen-mediated toxicity, propylparaben and butylparaben were administered subcutaneously at doses of up to 35 mg/d to pregnant mice during days 1 to 4 of pregnancy. This study found no adverse reproductive or other effects in mice, whereas the positive control substance, 17 β -estradiol, produced the expected termination of pregnancy.⁴⁶ A developmental toxicity study of butylparaben administered to rats at doses of up to 1000 mg/kg/d failed to reveal adverse reproductive effects.⁴⁷ Similar results were obtained in a study undertaken to resolve the conflicting published evidence about the *in vivo* effects of propylparaben on the male reproductive tract in juvenile rats and to investigate other parameters, including low-dose exposure, recovery, exposure, and hormone analysis. The protocol was based on those of published studies designed to investigate the effects of parabens on the male reproductive system, with male rats exposed to comparable oral doses from weaning to adulthood. There was no evidence of an effect of propylparaben on the weight of the male reproductive organs, epididymal sperm parameters, hormone levels, or

histopathology. The dose of 1000 mg/kg/d was the no-observed adverse effect level, corresponding to a maximum plasma concentration of 12,030 ng/mL and exposure to 47,760 ng·h/mL (area under the curve, 0–8 hours) at the end of the treatment.⁴⁸ The overall evidence, as well as the consensus of a number of expert reviews, suggests that parabens pose little or no risk of adverse reproductive effects *in vivo*.^{3,4,49–51}

EFFECT OF PARABENS ON ADIPOCYTE DIFFERENTIATION

Research on the effects of parabens on health is limited, and the effects of parabens on adipogenesis have not been systematically studied. Hu et al⁵² report that parabens promote adipogenesis (or adipocyte differentiation) in murine 3T3-L1 cells, as revealed by adipocyte morphology, lipid accumulation, and messenger RNA expression of adipocyte-specific markers. The adipogenic potency of parabens is increased with increasing length of the linear alkyl chain in the following potency ranking order: methylparaben < ethylparaben < propylparaben < butylparaben. The adipogenic effects of parabens are mediated through the glucocorticoid receptor and/or the peroxisome proliferator-activated receptor γ . These results suggest that parabens could contribute to the obesity epidemic, and the role of parabens in adipogenesis *in vivo* needs to be examined further.

PARABENS ACTIVITY IN HUMAN SUBJECTS

As discussed, most data published in the last decade from *in vivo* and *in vitro* studies show a very weak estrogenic activity of the parabens, but clinical data in human subjects are lacking. The study by Janjua et al³⁹ analyzed dermal absorption in human subjects. Twenty-four healthy volunteers were exposed daily for 1 week to a cosmetic formulation containing 2% of butylparaben, 2% of diethyl phthalate, and 2% of dibutyl phthalate. Serum measurements showed that butylparaben was detectable with a concentration peak of 135 μ g/L, but no effect was noticed on multiple hormone levels (luteinizing hormone, estradiol, thyroid-stimulating hormone). It should be noted that the concentration of parabens in this study was much higher than the 0.4% allowed in cosmetic products and is not reflective of the standard usage of parabens.

Regarding the effect of parabens on the male reproductive system, 1 study in human subjects by Meeker et al⁵³ investigated the relationship between urinary concentrations of parabens, serum hormone levels, and semen quality parameters. They collected samples from male partners ($n > 132$) attending an infertility clinic. No evidence was found of a relationship between parabens and hormone levels, sperm count, or motility. However, a significant association between sperm DNA damage (measured by Comet assay) and butylparaben was observed. Limitations of this study included a high temporal variability in paraben exposure levels and a relatively small sample size resulting in low statistical power.

Two recent studies evaluated a potential association between urinary paraben concentrations and markers of oxidative stress and inflammation. Kang et al⁵⁴ showed an association between urinary levels of butylparaben and a marker of oxidative damage (8-hydroxydeoxyguanosine). Watkins et al⁵⁵ showed that urinary isoprostane, a reliable marker of oxidative stress, was associated with elevated urinary levels of butylparaben and propylparaben; however, an increase in butylparaben was contradictorily associated with a decreased C-reactive protein, a nonspecific marker of inflammation.

Most epidemiologic studies performed in humans carried significant limitations. The identified correlations might be coincidental, and studies with larger sample sizes are needed to properly assess causality. Many confounders (systemic disease, viral infection, medication) may explain elevated nonspecific markers of oxidative stress and inflammation. However, this weak yet significant relationship warrants more investigation. Most data published in the last decade support a weak estrogenic activity of parabens, but clinical data in human subjects are lacking. Studies are designed under specific in vitro and in vivo experimental protocols that are not reflective of human effects mainly because they fail to prove hormonal activity in humans and fail to consider the metabolism, degradation, and elimination of parabens in human subjects.⁵⁶

CONCLUSION

All this new information is ground enough for concern. The World Health Organization Expert Committee on Food Additives has recommended that, in view of the adverse effects in male rats (reproductive toxicity associated with endocrine effects), propylparaben should be excluded from the group Acceptable Daily Intake for parabens used in food.⁵⁷ The same evaluation noted the withdrawal of specification for butylparaben on similar grounds.

Given that the estrogenic effect is dose related, Routledge et al¹⁶ determined that methylparaben was 2.5 million times and butylparaben was 10,000 times less potent than 17 β -estradiol. Any effect caused by the doses of parabens received from topical consumer products is likely to be insignificant compared with natural estrogens. The American Cancer Society has concluded that there is no good evidence to support a claim that use of cosmetics such as antiperspirants increases an individual's risk of developing breast cancer.⁵⁸ Epidemiological studies evaluating underarm cosmetics and breast cancer are conflicting, and although paraben exerts very weak estrogenic activity in vitro and in vivo, human clinical data are lacking, and there is insufficient scientific evidence to establish causality between parabens and breast cancer. However, tissue distribution of parabens is unknown, as well as the effects of long-term exposure. New evidence seems to show that they may not be as safe as we used to think, and larger, prospective, epidemiological, and toxicological studies are needed. If the results of these future studies eventually establish a link between parabens and breast cancer or other endocrine-disturbance disorder, the industry will have no choice but to turn away from these preservatives.

The numerous articles published by Darbre and her collaborators already have made an impact in the general public, and many cosmetic companies have reacted by substituting parabens with other preservatives such as the isothiazolinones. The consequences for dermatologists are obvious: we are facing an epidemic of allergic contact dermatitis to methylisothiazolinone and subsequently more work in the patch test clinic.

ACKNOWLEDGMENTS

The authors wish to thank Dr Joe Schwarcz, PhD, Department of Chemistry, McGill University, for reviewing the article.

REFERENCES

1. Kang YH, Parker CC, Smith AC, et al. Characterization and distribution of phenolics in carrot cell walls. *J Agric Food Chem* 2008;56(18):8558–8564.
2. Sellappan S, Akoh CC, Krewer G. Phenolic compounds and antioxidant capacity of Georgia-grown blueberries and blackberries. *J Agric Food Chem* 2002;50(8):2432–2438.
3. Cashman AL, Warshaw EM. Parabens: a review of epidemiology, structure, allergenicity, and hormonal properties. *Dermatitis* 2005;16(2):57–66.
4. Cosmetic Ingredient Review Expert Panel. Final amended report on the safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben as used in cosmetic products. *Int J Toxicol* 2008;27(suppl 4):1–82.
5. Castelain F, Castelain M. Parabens: a real hazard or a scare story? *Eur J Dermatol* 2012;22(6):723–727.
6. Bonnevie P. Øverfølsomhed for aetylparaoxybenzoat (Mycotlen). *Nord Med* 1940;6:684–685.
7. Jong CT, Statham BN, Green CM, et al. Contact sensitivity to preservatives in the UK, 2004–2005: results of multicentre study. *Contact Dermatitis* 2007;57(3):165–168.
8. Wilkinson JD, Shaw S, Andersen KE, et al. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002;46:207–210.
9. Svedman C, Andersen KE, Brandão FM, et al. Follow-up of the monitored levels of preservative sensitivity in Europe: overview of the years 2001–2008. *Contact Dermatitis* 2012;67:312–314.
10. Warshaw EM, Belsito DV, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2011–2012. *Dermatitis* 2015;26(1):49–59.
11. Gonçalves M, Goossens A. Whilst Rome burns: the epidemic of contact allergy to methylisothiazolinone. *Contact Dermatitis* 2013;68:257–258.
12. Castaneda-Tardana MP, Zug KA. Methylisothiazolinone. *Dermatitis* 2013; 24(1):2–6.
13. Council Directive of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (76/768/EEC). Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20100301>. Accessed September 7, 2015.
14. Karpuzoglu E, Holladay SD, Gogal RM Jr. Parabens: potential impact of low-affinity estrogen receptor binding chemicals on human health. *J Toxicol Environ Health B Crit Rev* 2013;16(5):321–335.
15. Kirchhof MG, de Gannes GC. The health controversies of parabens. *Skin Therapy Lett* 2013;18(2):5–7.
16. Routledge EJ, Parker J, Odum J, et al. Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic. *Toxicol Appl Pharmacol* 1998; 153:12–19.

17. Hossaini A, Larsen JJ, Larsen JC. Lack of oestrogenic effects of food preservatives (parabens) in uterotrophic assays. *Food Chem Toxicol* 2000;38(4):319–323.
18. Byford JR, Shaw LE, Drew MG, et al. Oestrogenic activity of parabens in MCF7 human breast cancer cells. *J Steroid Biochem Mol Biol* 2002; 80(1):49–60.
19. Darbre PD, Byford JR, Shaw LE, et al. Oestrogenic activity of isobutylparaben *in vitro* and *in vivo*. *J Appl Toxicol* 2002;22:219–226.
20. Darbre PD, Byford JR, Shaw LE, et al. Oestrogenic activity of benzylparaben. *J Appl Toxicol* 2003;23:43–51.
21. Darbre PD. Underarm cosmetics and breast cancer. *J Appl Toxicol* 2003;2(2):89–95.
22. Rageth CJ. One step forward in proving, that underarm cosmetics do not cause breast cancer. *Breast* 2005;14:85–86.
23. Darbre PD. Underarm antiperspirants/deodorants and breast cancer. *Breast Cancer Res* 2009;11(suppl 3):S5.
24. Darbre PD, Aljarrah A, Miller WR, et al. Concentrations of parabens in human breast tumours. *J Appl Toxicol* 2004;24(1):5–13.
25. Harvey PW, Everett DJ. Significance of the detection of esters of p-hydroxybenzoic acid (parabens) in human breast tumours. *J Appl Toxicol* 2004;24:1–4.
26. Golden R, Gandy J. Comment on the publication by Darbre et al. (2004). *J Appl Toxicol* 2004;24(4):297–299.
27. Jeffrey AM, Williams GM. The paper by Darbre et al. (2004) reports the measurement of parabens in 20 human breast tumors. *J Appl Toxicol* 2004;24(4):301–303.
28. Flower C. Observations on the paper by Darbre et al. (2004). *J Appl Toxicol* 2004;24(4):304–305.
29. Darbre PD, Pope GS, Aljarrah A, et al. Reply to Robert Golden and Jay Gandy. *J Appl Toxicol* 2004;24(4):299–301.
30. Darbre PD, Harvey PW. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. *J Appl Toxicol* 2008;28:561–578.
31. Lemini C, Jaimez R, Avila ME, et al. *In vivo* and *in vitro* estrogen bioactivities of alkyl parabens. *Toxicol Ind Health* 2003;19:69–79.
32. Oishi S. Lack of spermatotoxic effects of methyl and ethyl esters of p-hydroxybenzoic acid in rats. *Food Chem Toxicol* 2004;42:1845–1849.
33. Prusakiewicz JJ, Harville HM, Zhang Y, et al. Parabens inhibit human skin estrogen sulfotransferase activity: possible link to paraben estrogenic effects. *Toxicology* 2007;232:248–256.
34. Charles AK, Darbre PD. Combinations of parabens at concentrations measured in human breast tissue can increase proliferation of MCF-7 human breast cancer cells. *J Appl Toxicol* 2013;33:390–398.
35. Mirick DK, Davis S, Thomas DB. Antiperspirant use and the risk of breast cancer. *J Natl Cancer Inst* 2002;94:1578–1580.
36. McGrath KG. An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. *Eur J Cancer Prev* 2003;12:479–485.
37. Ye X, Kuklenyik Z, Bishop AM, et al. Quantification of the urinary concentrations of parabens in humans by on-line solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006; 844:53–59.
38. Ishiwatari S, Suzuki T, Hitomi T, et al. Effects of methyl paraben on skin keratinocytes. *J Appl Toxicol* 2007;27:1–9.
39. Janjua NR, Mortensen GK, Andersson AM, et al. Systemic uptake of diethyl phthalate, dibutyl phthalate, and butyl paraben following whole-body topical application and reproductive and thyroid hormone levels in humans. *Environ Sci Technol* 2007;41:5564–5570.
40. Frederiksen H, Jørgensen N, Andersson AM. Parabens in urine, serum and seminal plasma from healthy Danish men determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). *J Expo Sci Environ Epidemiol* 2011;21(3):262–271.
41. Sandanger TM, Huber S, Moe MK, et al. Plasma concentrations of parabens in postmenopausal women and self-reported use of personal care products: the NOWAC postgenome study. *J Expo Sci Environ Epidemiol* 2011;21(6): 595–600.
42. Oishi S. Effects of butylparaben on the male reproductive system in rats. *Toxicol Ind Health* 2001;17(1):31–39.
43. Oishi S. Effects of butyl paraben on the male reproductive system in mice. *Arch Toxicol* 2002;76(7):423–429.
44. Oishi S. Effects of propyl paraben on the male reproductive system. *Food Chem Toxicol* 2002;40(12):1807–1813.
45. Hoberman AM, Schreier DK, Leazer T, et al. Lack of effect of butylparaben and methylparaben on the reproductive system in male rats. *Birth Defects Res B Dev Reprod Toxicol* 2008;83:123–133.
46. Shaw J, deCatanzaro D. Estrogenicity of parabens revisited: impact of parabens on early pregnancy and an uterotrophic assay in mice. *Reprod Toxicol* 2009;28(1):26–31.
47. Daston GP. Developmental toxicity evaluation of butylparaben in Sprague-Dawley rats. *Birth Defects Res B Dev Reprod Toxicol* 2004;71(4):296–302.
48. Gazin V, Marsden E, Marguerite F. Oral propylparaben administration to juvenile male Wistar rats did not induce toxicity in reproductive organs. *Toxicol Sci* 2013;136(2):392–401.
49. Golden R, Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. *Crit Rev Toxicol* 2005;35(5):435–458.
50. Witorsch RJ, Thomas JA. Personal care products and endocrine disruption: a critical review of the literature. *Crit Rev Toxicol* 2010;40(suppl 3):1–30.
51. Scialli AR. Reproductive effects of the parabens. *Reprod Toxicol* 2011; 32(1):138–140.
52. Hu P, Chen X, Whitener RJ, et al. Effects of parabens on adipocyte differentiation. *Toxicol Sci* 2013;131(1):56–70.
53. Meeker JD, Yang T, Ye X, et al. Urinary concentrations of parabens and serum hormone levels, semen quality parameters, and sperm DNA damage. *Environ Health Perspect* 2011;119(2):252–257.
54. Kang S, Kim S, Park J, et al. Urinary paraben concentrations among pregnant women and their matching newborn infants of Korea, and the association with oxidative stress biomarkers. *Sci Total Environ* 2013; 461–462:214–221.
55. Watkins DJ, Ferguson KK, Anzalota Del Toro LV, et al. Associations between urinary phenol and paraben concentrations and markers of oxidative stress and inflammation among pregnant women in Puerto Rico. *Int J Hyg Environ Health* 2015;218(2):212–219.
56. Soni MG, Carabin IG, Burdock GA. Safety assessment of esters of p-hydroxybenzoic acid (parabens). *Food Chem Toxicol* 2005;43(7):985–1015.
57. Adegoke G, Bend J, Bolger M, et al. *Propylparaben*. Sixty-seventh report of the Joint FAO/WHO Expert Committee on food additives. 2006;30–32. Available at: <http://www.who.int/ipcs/publications/jecfa/reports/trs940.pdf>. Accessed September 7, 2015.
58. American Cancer Society. *Antiperspirants and breast cancer risk*. Available at: <http://www.who.int/ipcs/publications/jecfa/reports/trs940.pdf>. Accessed September 7, 2015.