Phthalates have been defined by the EPA and FDA as diesters of low-molecular-weight alcohols and orthophthalic acid. By contrast, phthalate enteric polymers are mono-esters of orthophthalic acid, and the alcohol is present in the form of a polymer backbone. These differences in structure translate to differences in chemical properties and biological activities.

Phthalate enteric polymers are used to form enteric coatings. These coatings are applied to tablets or capsules to delay release: The coatings remain intact in the stomach but dissociate and release the contents of the drug product in the small intestine. Their prime purpose is to delay the release of the active pharmaceutical ingredient (API), which may be inactivated in the stomach or cause irritation of the gastric mucosa.

Commonly used enteric polymers include cellulose acetate phthalate (CAP), CAP aqueous dispersion, hypromellose phthalate (HPMCP), and polyvinyl acetate phthalate (PVAP). The common term in the nomenclature of these high-molecular-weight polymers is the word “phthalate” because these enteric polymers have been modified by esterification with orthophthalic acid groups. The enteric polymers are large molecules, with typical molecular weights in the range of 60,000 to 130,000 daltons.

Unlike phthalate enteric polymers, esters of orthophthalic acid with low-molecular-weight alcohols, such as dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP), have been developed and used commercially as plasticizers. DBP and DEHP are small molecules with molecular weights of only 278 and 390, respectively.

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The enteric polymers are very different from DBP and DEHP based on properties such as chemical structure and molecular weight and have completely different functions. Recent data suggest that many of these phthalate plasticizers may pose significant hazards to human health and the environment. Despite substantial differences in the chemical properties between the phthalate plasticizers and enteric polymers containing orthophthalic acid, recent safety concerns for the phthalate plasticizers have prompted some scientists to question whether the polymers that are used as excipients for enteric coatings of pharmaceuticals pose similar safety concerns. Accordingly, we set out herewith to clarify the applications of the enteric polymer excipients, explain why the safety concerns relating to phthalate plasticizers do not apply to these enteric polymers, and summarize the data that support the continued safe use of these materials.

Nomenclature

The term “phthalate” has been defined by the EPA (2012 EPA Action Plan) and other regulatory agencies to identify diesters of orthophthalic acid, also called simply phthalic acid, an aromatic dicarboxylic acid in which the two carboxylic acid groups are located on adjacent carbons (positions 1 and 2) in the benzene ring. Both DBP and DEHP are examples of such phthalates, and these phthalates are chemically and toxicologically distinct from diesters of iso- or tere-phthalic acids, which are not considered “phthalates” as defined by the EPA. There are important distinctions regarding iso- and tere-phthalic acid derivatives with the orthophthalates. The colloquial use of “phthalates” in several publications has created unsubstantiated and erroneous safety concerns. The specific toxicological concern with DEHP and DBP arises from their metabolic conversion to their corresponding monoesters (Thomas et al., 1982; Curto and Tho-
As a case in point, consider the inaccurate and misleading statements in the article “Identification of phthalates in medications and dietary supplement formulations in the United States and Canada” by Kelley et al. (EHP 120(3), March 2012), which has contributed to the confusion. In that article, Kelley et al. inappropriately refer to three polymers (PVAP, HPMCP, and CAP) as “phthalates” and inappropriately imply that they too are “phthalates” simply because they have the word phthalate in their names.

HPMCP, PVAP, and CAP are polymers that have been modified by esterification with orthophthalic acid groups. These high-molecular-weight polymers differ markedly from the short-chain alcohols used to produce DEHP and DBP, and thus these polymers are not orally bioavailable and their chemical properties are very different. In fact, any metabolism of these phthalate ester polymers that might occur would not produce the monoesters about which people are concerned.

**Regulatory guidance on phthalate excipients**

The December 2012 FDA “Guidance for Industry—Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products” recommended that the pharmaceutical industry avoid the use of two specific phthalates as excipients in CDER-regulated drug and biologic products: DBP and DEHP. In the Guidance, the FDA is careful to note that its recommendations apply only to DBP and DEHP. Nonetheless, suppliers of excipients have received inquiries from customers about the applicability of the Guidance to unrelated products that include “phthalate” in their chemical name. This confusion is not limited to the marketplace, but is seen even in the scientific literature.

In the EMAs draft “Guideline on the use of phthalates as excipients in human medicinal products,” the Agency proposes “Permitted Daily Exposures (PDE) values of 0.01, 4 and 2 mg/kg/day for DBP, DEP and PVAP respectively.” The EMA also concluded that there was “no data indicating that the presence of CAP and HPMCP in human medicinal products constitutes a potential risk for human safety.” New GLP-compliant safety studies for PVAP from Colorcon, submitted to and under evaluation by EMA, support a significantly higher PDE for PVAP.

**Enteric polymer applications**

Enteric polymers (phthalate ester polymers) are more soluble at a higher pH than at a low pH. The deleterious effects of stomach acid on a variety of orally administered pharmaceutical products have been known for decades. The enteric coating remains intact in acidic media and dissolves in the relatively neutral environment of the intestines, where dissolution and absorption of the products occur. Some of the earliest materials to be developed for this purpose were polymers containing orthophthalic acid as a substituent, and many of these same materials continue to be used extensively today.

The typical application of the enteric polymer coating is approximately 5 to 10 percent of the tablet or capsule core’s weight. Phthalate ester polymers may also be used in the manufacture of modified-release products, e.g. extended- or prolonged-release formulations. Depending on the mechanism of prolonging or extending the release of the drug, the amount of polymer in the final formulation may approach 30 percent.

**Safety information in phthalate enteric polymer excipients**

CAP. In the first chronic safety studies for CAP, conducted in 1944, groups of rats and dogs were fed CAP daily for a period of 1 year (Hodge, 1944). In the rat study, four groups of 20 rats each were fed diets containing 0, 5, 20, and 30 percent CAP daily for one year. The rats on high intakes of CAP showed a reduction in growth rate that increased with the dosage. On autopsy, the rats were in good condition and no abnormalities were observed except that the average stomach weight tended to increase with higher doses of CAP. From histological examinations, no consistent pathological changes were demonstrated. High doses of CAP in the diet tended to produce a mucilaginous character of the material in the intestinal lumen. From these observations it is concluded that the high levels of CAP in the diet of rats interfere quantitatively and mechanically with the absorption of food. No toxic action of CAP has been found in rats (Hodge, 1944). In the dog study, three groups of two dogs each were fed 1, 4, and 16 grams, respectively, of CAP for 1 year. The dogs remained in excellent health and condition throughout the experiment and no consistent pathological changes were discovered at autopsy. There was no evidence of any toxic effects of CAP under these conditions, and from these studies, it was determined that in general CAP seems to be remarkably inert as a compound of the diet (Hodge, 1944).

**CAP aqueous dispersion.** Studies were performed to assess the safety of Aquateric, an enteric coating that includes a CAP aqueous dispersion. The studies comprised subchronic and developmental toxicity studies in rats (Kotkoskie et al., 1999), and a series of genotoxicity studies (Batt and Kotkoskie, 1999). In the subchronic toxicity study, groups of Sprague-Dawley rats (20/sex/group) were fed diets for 90 days that contained 0 (control), 5,000, 25,000, or 50,000 ppm of an Aquateric aqueous enteric coating that was 67.9 percent. No mortality, clinical signs, toxicity, or adverse toxicological effects were observed in any treatment group following evaluations of hematology, serum chemistry, body weights, and feed consumption, as well as ophthalmological examinations and histological evaluations of tissues. The no-observed-adverse-effect level (NOAEL) for CAP was determined to be in excess of 50,000 ppm of Aquateric.

In the developmental study, groups of pregnant Sprague-Dawley rats (25/group) were fed diets that contained 0 (control), 5,000, 25,000, or 50,000 ppm of the Aquateric coating.
on gestational days 6 through 15. No evidence of maternal toxicity, embryotoxicity, or fetotoxicity was noted. Based on the results of these studies, the NOAEL for CAP was determined to be greater than 50,000 ppm of Aquateric.

In the Ames assay, the Aquateric enteric coating was not mutagenic when tested in Salmonella typhimurium cell strains TA98, TA100, TA1535, TA1537, and TA1538, with or without metabolic activation. A mouse lymphoma assay was conducted using concentrations that ranged from 116 to 2,000 µg/mL or 116 to 1,250 µg/mL in the absence or presence of metabolic activation, respectively. No increase in mutation frequency was observed at any concentration tested. A mouse micronucleus assay was conducted using a single oral dose of 7,200 mg/kg, which represented a dose of CAP of 5,000 mg/kg, and bone marrow was harvested 24, 48, or 72 hours after treatment. The data indicated that there were no significant increases in the number of bone marrow micronucleated polychromatic erythrocytes at any time following the administration of Aquateric.

HPMCP. The following studies were conducted for HPMCP via oral administration.

In an acute toxicity study in rats (Kitagawa et al., 1970), LD₅₀ could not be determined (presumably over 15 g/kg). In a sub-acute toxicity study in rats for 30 days—dosing as much as 10 g/kg/day—there were no adverse effects (Kitagawa et al., 1970).

In a chronic study in rats, dosing as much as 6 g/kg/day for 6 months, there was no remarkable toxicity (Kitagawa et al., 1970). Another chronic study, this one using dogs dosed as much as 3 g/kg/day for 53 weeks, was conducted (Woodward Research, 1974). There were no changes that could be ascribed to the administration of HPMCP, with the exception of frequent soft stools for dogs receiving 3 g/kg/day and a less frequent occurrence in dogs receiving 1.5 g/kg/day. From a teratogenicity study using rats and mice in which dosing was 2.4 g/kg (rat) and 4 g/kg (mouse), it can be concluded that HPMCP produces no malformation (Ito and Toida, 1972).

Two ADME studies in rats were conducted using 14C-labeled HPMCP (Kitagawa et al., 1971, 1974). One was with 14C labeled to methoxy groups of the HPMCP backbone, and dosing was 3 g/kg. Approximately 92 to 96 percent of the doses were excreted in feces within 96 hours, and less than 1 percent of HPMCP was excreted in urine. Another study, conducted using 14C labeled to the phthalyl groups at a dose of 1.3 g/kg, showed that excretion in the urine was 0.7 percent for male and 1.2 percent for female rats during 72 hours, whereas excretion in the feces was 95 percent for male and 91 percent for female rats. These studies indicated poor oral absorption of this high-molecular-weight polymer.

PVAP. More recent safety studies were conducted on PVAP, including an acute oral toxicity study, a 90-day subchronic dietary study in rats, a developmental toxicity study in rats, and two genotoxicity tests. These studies have been submitted for publication in peer-reviewed journals.

The acute oral toxicity of PVAP was assessed in male and female rats that received PVAP by gavage at the maximum (limit) dose. Under the conditions of the study, the acute oral LD₅₀ of PVAP was estimated to be greater than 5,000 mg/kg in the rat.

A 90-day subchronic dietary study was conducted to evaluate the potential toxicity of PVAP when administered in the diet to Sprague-Dawley CRL: CD (SD) rats (20/sex/group) at a dietary concentration of 0.75 percent, 1.5 percent, and 5.0 percent for a minimum of 90 days. Control animals (20/sex) received an untreated standard laboratory diet. Daily administration of PVAP in the diet was well tolerated in male and female rats up to a concentration of 5 percent. No PVAP-related toxicity or mortality was observed. Based on these results, the NOAEL was the 5 percent dietary concentration.

A developmental toxicity study was conducted to assess the potential toxicity of PVAP in CRL: CD (SD) presumed-pregnant female rats (from implantation to closure of the hard palate). There were no consistent, treatment-related, dose-dependent, statistically significant adverse effects on any of the maternal and fetal parameters evaluated. Therefore, the maternal and developmental NOAEL of PVAP is the highest concentration administered: 3.0 percent.

A bacterial mutation test and a chromosome aberration test were performed to evaluate the potential genotoxicity of PVAP. There was no evidence of genotoxic activity of PVAP in the in vitro bacterial mutation test and no evidence of clastogenicity in the in vitro chromosome aberration test for induction of chromosome damage.

**Conclusion**
Collectively, the safety data indicate that enteric polymers are inert materials when incorporated into the diets of laboratory animals. Enteric polymers have been used for many decades and generally there have not been adverse reaction reports. Thus, all available data support the safety of enteric polymers for use as pharmaceutical excipients.

IPEC-Americas requested that the FDA explain that its Guidance, “Limiting the Use of Certain Phthalates as Excipients,” applies to only DBP and DEHP and not to commonly used excipients such as CAP, PVAP, and HPMCP. IPEC-Americas also requested that EMA not impose a PDE of 2 mg/kg/day of PVAP because more recent safety data are available, and the more recent PVAP studies support a significantly higher PDE for PVAP.

Phthalate ester polymers are substances in which the phthalate moiety is esterified with polymers, not the short-chain alcohols that are used in the manufacture of DBP and DEHP and that contribute to substantial differences in the physical/chemical properties between the two types of materials. Pharmaceutical manufacturers selecting phthalate ester polymers for use in their regulated products need to distinguish between the class of molecules that is...
the subject of the Draft Guidances and those that are not.

IPEC-Americas has presented several examples to illustrate the danger of using a common name to incriminate a group of structurally diverse compounds simply because they share one common structural feature (phthalate); doing so creates unsubstantiated safety concerns where none exists. The above toxicological test data indicate a low level of oral toxicity for these structurally diverse polymers; thus, all available data support the safety of enteric polymers for use as pharmaceutical excipients.

**References**

International Pharmaceutical Excipients Council of the Americas (IPEC-Americas). Correspondence: Defining “Phthalates”. Environmental Health Perspectives. 120(11), November 2012.  

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