# Phthalates in 5-Aminosalicylates:

## Informing Therapeutic Choice and Minimizing Risk

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*Abstract*

*5-Aminosalicylates (5-ASAs) are considered first-line therapy for mild to moderate ulcerative colitis because of their proven effectiveness and safety profile, even in pregnancy. One formulation, however, contains dibutyl phthalate (DBP) in its coating. Though DBP may cause disruptions in utero reproductive development and other congenital abnormalities in rodents, it is unclear whether it leads to physiologically significant fetal abnormalities in humans. The US Food and Drug Administration has changed its classification for DBP-containing 5-ASAs from pregnancy category B to pregnancy category C to reflect a greater degree of uncertainty regarding its effect in humans. For pregnant women with ulcerative colitis, the most important message is to take their inflammatory bowel disease (IBD) medications to prevent disease relapse, which may have the most adverse effects on pregnancy. Physicians should, however, discuss with young women who are taking 5-ASA with DBP the benefits and risks of switching to another formulation of 5-ASA without the DBP compound.*

*Key words: phthalates, 5-aminosalicylate, ulcerative colitis, dibutyl phthalate, pregnancy*

Ulcerative colitis (UC) is a chronically relapsing condition involving inflammation of the colon that may lead to substantially impaired quality of life and colectomy in up to one-third of patients. The goals of medical management are to achieve and maintain clinical remission and to prevent long-term complications of long-standing disease. 5-Aminosalicylates (5-ASAs) are the first-line therapy for mild to moderate UC given their excellent safety profile, even during pregnancy.[1] There are various formulations of 5-ASA that enable them to be released at different sites of the gastrointestinal tract (Figure 1). One of these delivery mechanisms is pH dependent, with a release at a pH of 7; this assures that the release occurs predominantly in the colon, which is most effective in UC. Under the trade name Asacol a type of mesalazine, this formulation uses Eudragit S enteric coating, which also contains dibutyl

phthalate (DBP).[2] The use of phthalates as excipients, which are inactive carriers for the active ingredients of a medication, has recently undergone scrutiny because certain phthalates may be associated with endocrine and reproductive toxicities.

## Phthalates and Fetal Development

Phthalates are plasticizers that are used to increase the flexibility, transparency, and durability of plastics.[3] They are ubiquitous and are found in items such as personal care products, packaging, medications, medical equipment and tubing, glues and paints, plastic toys, and a variety of household products including vinyl upholstery, shower curtains, food containers, cleaning materials, and flooring. Because they are not covalently bonded, these chemicals are easily leached into food and the environment. Most Americans tested by the Centers for Disease Control and Prevention have demonstrated measurable levels of phthalates in their urine that have been acquired through ingestion, inhalation, and, less commonly, absorption into the skin. The United States has prohibited the use of certain phthalates (DBP, di[2-ethylhexyl] phthalate [DEHP], and benzyl butyl phthalate [BBP]) in children's toys, and Europe has prohibited their use in cosmetics.

Animal studies have shown that certain phthalates, including DEHP, DBP, and BBP, have been associated with severe and irreversible abnormalities in fetal reproductive development, particularly in male fetuses. DBP is the phthalate most relevant for patients with inflammatory bowel disease (IBD). In studies of rats, in utero exposure to DBP at dosages nearly 17-fold the maximum recommended dosage in humans, based on surface area, was associated with a disruption of androgenic-dependent reproductive development among male offspring. At progressively higher dosages of DBP exposure (84-fold higher than human dosages), cryptorchidism, hypospadias, testicular injury, atrophy or agenesis of accessory sex organs, reduced sperm production, and decreased anogenital distance (AGD) were observed. Congenital defects such as cleft palate and skeletal abnormalities occurred in rat models at dosages more than 100-fold those recommended for humans.[2]

It remains unclear whether phthalates have similar detrimental effects on human reproductive development. Several studies have shown an association between in utero phthalate exposure, as measured by metabolites in the urine, and reduced AGD in male fetuses.[4,5] AGD serves as an indicator of intrauterine androgenic

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**Key Point**

*Dibutyl phthalate (DBP) is found in the coating of certain formulations of 5-ASA, and in rodents has been shown to be associated with developmental and congenital abnormalities.*

exposure and is frequently measured in reproductive toxicity studies. There have also been reports of reduced penis width and length with higher phthalate exposure.[6] However, the clinical significance and implications of these physical variations have not been determined. One study showed an inverse relationship between phthalate exposure and degree of testicular descent.[6] However, cryptorchidism has not been linked to high levels of phthalates in humans. A series of studies also suggested that exposures to several phthalates may lead to low sperm concentration and motility among men seen in fertility clinics.[7–9] These findings, however, have not been reproduced in the general population.

GIVEN THE POTENTIAL EFFECTS ON REPRODUCTIVE DEVELOPMENT IN MALE FETUSES, PREGNANT WOMEN DESERVE SPECIAL CONSIDERATION WHEN DECIDING WHICH 5-ASA FORMULATION TO PRESCRIBE.

## Use of 5-ASAs in Pregnancy

While there is limited evidence that exposure to certain phthalates may lead to aberrations in reproductive outcomes, there is no unequivocal evidence that administration of Asacol in recommended dosages leads to physiologically significant congenital abnormalities. However, it appears that the ingestion of 5-ASA with the Eudragit S coating may lead to an appreciable absorption of DBP. In one US study, six individuals taking 5-ASA exhibited mean concentrations of DBP metabolites that were 50-fold those in non-users of 5-ASA.[10] One-third of those individuals had concentrations that exceeded the upper limit of the recommended dosage according to the US Food and Drug Administration (FDA). Given the potential effects on reproductive development in male fetuses, pregnant women deserve special consideration when deciding which 5-ASA formulation to prescribe. Despite the potential risk, retrospective and prospective studies of over 600 women who were administered 5-ASA, but not specifically Asacol, did not find an increased rate of congenital abnormalities relative to the general population.[11] Based on the available data, FDA has classified Asacol as a pregnancy category C drug, which reflects that adverse effects have been observed in animal testing but not proven in humans. It is important to emphasize that category C drugs may still be used in pregnancy when the benefits may outweigh the potential risks.[2]

Most gastroenterologists would agree that achieving and maintaining remission of UC during pregnancy with an effective drug that is classified as category C outweighs the risks. However, the decision to use Asacol should also take into account that most other 5-ASA formulations remain in the lower-risk category B. It should be noted that FDA released a preliminary draft statement in March of 2012 in which it recommended the substitution of inactive carrier agents that contained DBP and DEHP in prescription and non-

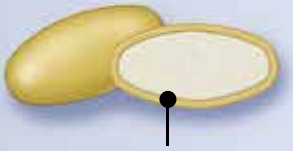
**Key Point**

*There are several formulations of 5-ASA that do not contain DBP.*

Figure 1:
**5-ASAs as Therapy for Ulcerative Colitis**

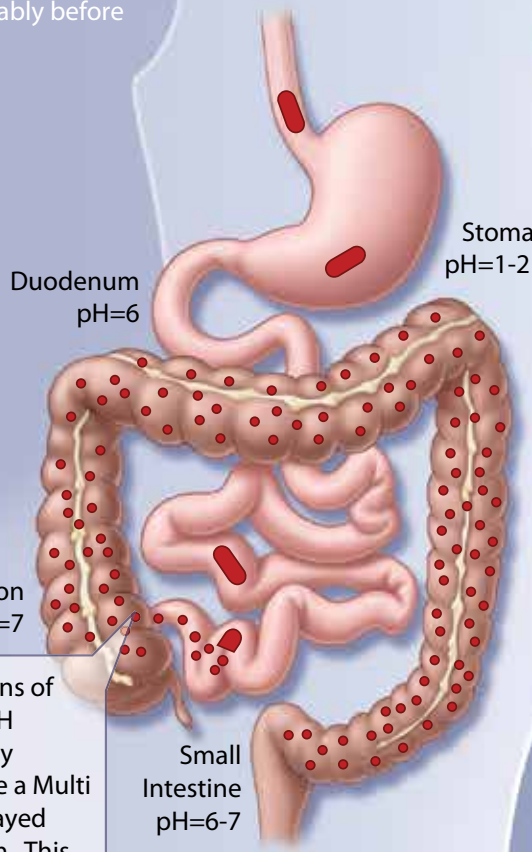
**Asacol** with Eudragit S coating (containing DBP)

**Mezavant** (coating not containing DBP)



**Salofalk** with Eudragit L coating (not containing DBP)

**Women of child-bearing age** who are taking a DBP-containing 5-ASA should have a discussion regarding the benefits and risks of switching to another 5-ASA, preferably before pregnancy.




Various formulations of 5-ASA may have pH dependent delivery mechanisms or use a Multi Matrix System delayed release mechanism. This allows for release to occur primarily in the colon where it can be most effective in ulcerative colitis.

It is important to inform **pregnant women** taking Asacol of the potential risks of DBP, but to emphasize that these risks are outweighed by the risks incurred when not taking any medication to manage their ulcerative colitis. There are alternative 5-ASA drugs that do not incorporate DBP.

Animal studies have shown that certain phthalates, including DBP, have been associated with severe and irreversible abnormalities in fetal reproductive development. It remains unclear whether phthalates have similar detrimental effects on human reproductive development.

prescription drugs.[12] Salofalk is an alternative 5-ASA pH-dependent delayed-release formulation that releases in the colon and uses Eudragit L coating, which does not contain DBP. Mezavant is also released predominantly in the colon and has been found to have similar efficacy to Asacol in achieving and maintaining remission.[13,14] Thus, there are alternative formulations of 5-ASA that are as effective as Asacol but do not carry the safety concerns associated with DBP.

So what are the implications for the management of mild to moderate UC in pregnant women? Given the availability of multiple alternative 5-ASA formulations, pregnant women with UC who are being initiated on 5-ASA therapy should be prescribed a 5-ASA that does not contain DBP. Perhaps the more challenging clinical question is, should a pregnant woman who is already in remission while taking Asacol be switched to another 5-ASA? There is the theoretical risk that switching to another 5-ASA drug could precipitate a flare, which might be especially detrimental to the mother and fetus during pregnancy. This risk of relapse, which some of us have observed anecdotally, must be balanced by the potential but insufficiently proven risk of fetal harm associated with DBP. This decision should be made on an individual basis after carefully explaining the risks and benefits of staying on Asacol or switching to another 5-ASA formulation. Important information to convey to a pregnant patient who is taking Asacol is shown in Table 1.

**Table 1. Important Information to Convey to Your Pregnant Patient**

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| Asacol is a pregnancy category C drug, which means it can still be taken if the benefit of the drug outweighs the risk. |
| It contains dibutyl phthalate (DBP) in its enteric coating. |
| Animal studies at supra-physiological dosages suggest that DBP may be associated with developmental and congenital abnormalities. |
| DBP is associated with some indicators of endocrine disruption in humans (male fetuses), but the clinical significance is unclear. |
| There are alternative 5-aminosalicylate (5-ASA) medications that do not contain DBP. |
| Controlling inflammatory bowel disease activity is likely to have the greatest impact on pregnancy outcome. |
| The most important thing to remember is to take your medication to prevent relapse. |

## Key Points

5-Aminosalicylates (5-ASAs) are effective for the treatment of mild to moderate ulcerative colitis and are generally regarded as safe to use, even during pregnancy.

Dibutyl phthalate (DBP) is found in the coating of certain formulations of 5-ASA, and in rodents has been shown to be associated with developmental and congenital abnormalities.

Though phthalates have been shown to be associated with some indicators of reduced masculinization among male fetuses, there is insufficient evidence to prove that it leads to significant harmful effects.

There are several formulations of 5-ASA that do not contain DBP.

Asacol, which contains DBP, is categorized as a pregnancy category C drug, while most other 5-ASAs are in pregnancy category B.

A survey of pregnant women with IBD has shown that the vast majority are concerned that their IBD medications can cause harm to their fetus and lead to congenital abnormalities.[15] Only one-fifth were appropriately concerned that IBD disease activity could lead to adverse pregnancy outcomes. Most women expressed that that they would be willing to avoid taking medications and endure IBD symptoms if it meant reducing the risk to the fetus. Disconcertingly, nearly one-third who decreased or stopped their medications did not tell their doctors. Most considered rescue therapy with 5-ASA when relapse occurs to be a safer treatment strategy than maintenance therapy. A significant number of women reported stopping conventional medical therapy in favour of "herbal" or "organic" therapies because they deemed them to be safer. Furthermore, their adherence to conventional IBD medications was more influenced by family and friends and information given on drug inserts than by reassurance from their physicians. A key implication from this survey is that pregnant women with IBD require education and reinforcement that active disease is probably the most important driving factor for poor outcomes during pregnancy. Secondly, we should learn from the survey that women's perception of harm from medications is an important determinant of non-adherence.

In the past, we have always been very confident in reassuring women that 5-ASA therapy is safe during pregnancy. Even though the detrimental effects of DBP in humans may not be well established, pregnant women's mere perception of harm may be enough to lead them to stop their medication. It is important to emphasize to pregnant women that the safety profile has not changed in 5-ASA formulations that do not contain DBP.

The discussion surrounding the risks and benefits of medication can be emotionally charged during

**Key Point**

*Asacol, which contains DBP, is categorized as a pregnancy category C drug, while most other 5-ASAs are in pregnancy category B.*

## Clinical Pearls

It should be emphasized to pregnant women that taking medications for their inflammatory bowel disease is important because the disease has a strong impact on, not just their health, but the health of their fetus too.

Women of child-bearing age who are taking a DBP-containing 5-ASA should have a discussion regarding the benefits and risks of switching to another 5-ASA, preferably before pregnancy.

pregnancy. Thus, the ideal circumstance under which to have this conversation is prior to pregnancy—with women of child-bearing age. It is a reasonable approach to not use 5-ASA drugs with DBP in this group of women so as to avoid having to make the difficult decision of whether to switch them to another 5-ASA when they are pregnant. For child-bearing women already taking Asacol, it may be prudent to initiate discussions on the risk of DBP exposure should they become pregnant. Switching 5-ASA formulations may carry a hypothetical and small possibility of relapse, and this risk is best borne prior to pregnancy.

## Conclusion

Though there has been recent increased scrutiny over 5-ASA formulations that contain DBP, patients should be reminded that the 5-ASA class of drugs are effective for achieving and maintaining remission. The safety of 5-ASA drugs other than Asacol remains unchanged. It is important to inform pregnant women taking Asacol of the potential risks of DBP, but to emphasize that these risks are far outweighed by the risks effected by not taking any medications, and that there are alternative 5-ASA drugs that do not incorporate DBP.

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