A literature review of the use of phenol for nail matrix ablation on pregnant and breastfeeding patients: implications for safe use

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Background Nail surgery using phenol to chemically ablate the nail matrix is a technique that has been performed for many years. The phenolic technique of nail surgery has been refined and established as a safe and effective procedure. Although it is used in small quantities podiatrically, phenol is readily absorbed through multiple routes such as ingestion, dermal absorption, and inhalation - the latter two being the most likely in podiatric practice. However, given its pervasiveness as a caustic agent in nail surgery, there is a paradoxically small narrative on the safety aspects of phenol's use in pregnant and breastfeeding patients. This paper reviews the available literature to provide a narrative response to this concern.

Method A literature search to identify research evidence from electronic databases and reference lists was performed. Evidence was also sought using Google Scholar free text keywords. A narrative review of the literature was then performed, with agreement from all authors.

Discussion Although patient safety concerns have been raised for the clinical use of a range of phenols, humans are environmentally exposed to such compounds in food, cosmetics, plastics, and resins. For the general population, cigarette smoke and smoked food products are the most common sources of phenol exposure. The data on phenol exposure during nail surgery and potential health consequences to the foetus are discussed.

Conclusion Following calculations for the potential absorption of phenol via an EZ swab, the authors suggest that the purported risks associated with the podiatric use of phenol are overly cautious given that there is no clear association between occupational exposure to phenol and adverse pregnancy outcomes. Although phenols are ubiquitous in the environment, these exposures have previously not been compared to those of phenol matrixectomy. Future research in this area would be highly beneficial, for example, the urinalysis of phenol before and after nail surgery in non-pregnant females.

Keywords: nail surgery, phenol, pregnancy, breastfeeding, safe use, teratogenic

The use of phenol to chemically ablate the nail matrix of ingrown toenails is a technique that has been performed for many years. Dagnall reports that this procedure was attributed to the British Army officer Major Holmes by Captain Porter in 1901 [1]. The technique was further documented by Boll [2], but its current popularity is a result of the work of Nyman in 1956 [3]. The phenolic technique of nail surgery has been refined and established as a safe and effective procedure, with the literature showing its effectiveness in preventing the recurrence and regrowth of an ingrown toenail [4].

Phenol is readily absorbed through multiple routes such as ingestion, dermal absorption, and inhalation [5] - the latter two being most likely to occur in podiatry. Environmental exposure to phenolic compounds is widespread for the general population [6,7]. Foetuses are especially vulnerable to environmental contaminants, and thus it is of particular importance to assess prenatal and early life exposure to such compounds [7–13]. More literature exists for the safety aspects surrounding the use of local anaesthesia in pregnant and breastfeeding patients; however, there is a clear concern in the United Kingdom's podiatric profession over the
relative safety of phenol use for these patients with concerns specifically relating to its risk of teratogenicity [14]. Given the common usage of phenol as a caustic agent in nail surgery, other medical and aesthetic procedures, and the reluctance to perform incisional (non-phenolic) nail surgery [15] there is a paradoxically small narrative on the compound's safety profile. This paper reviews the available literature and provides a narrative response to this concern.

**Phenol**

The phenols are organic compounds containing one (or more) hydroxyl (OH) groups directly attached to an aromatic hydrocarbon group. The simplest phenol - and the one used podiatristically has the chemical formula C₆H₅OH (see Fig. 1). It is a colourless-to-white solid with a sweet, acrid odour. Originally named carbolic acid, phenol was first isolated from coal tar in 1834 by the German chemist Friedlieb Runge [16,17]. Phenol reacts with strong bases to form alkali metal salts, known as phenoxydes, and with acids to produce esters. Phenol is soluble in alcohol but only partially soluble at room temperature. In the presence of oxygen from the air, phenol slowly oxidises to produce dark mixtures containing 1, 4-diketones called quinines [16].

![Figure 1 Phenol](https://en.wikipedia.org/wiki/Pronunciation)

Phenol has moderate acute toxicity for mammals. A range of adverse effects have been well-documented following accidental and over-exposure by dermal, oral, or intravenous routes. After absorption, phenol is rapidly distributed to all tissues [18]. There is limited data available on the carcinogenicity of phenol in humans; thus, the International Agency for Research on Cancer (IARC) concluded that phenol is not classifiable as to its carcinogenicity in humans [19]. Phenol is considered an in-vivo somatic mutagen [19] and has been identified as a developmental toxicant in studies with rats and mice [18] but little data regarding phenol's reproductive or developmental effects in humans is available. Small epidemiological studies have been carried out and have shown no clear association between occupational exposure to phenol and adverse pregnancy outcomes [19]. In August 2021, a United Kingdom National Patient Safety Alert was issued for the elimination of bottles of liquefied phenol. This was due to its history of being mixed up for other medications and the risks associated with spills [20]. However, its podiatric use will continue in the form of EZ-Swabs [21] which contain 0.175-0.2ml of phenol at 85-100% concentration.

**Method**

An initial Google Scholar literature search suggested that little information was available in the UK podiatric lexicon to answer questions of phenol safety for pregnant and breastfeeding mothers. The authors, therefore, performed a literature search that involved identifying research evidence from the following sources:

- Electronic databases
- Reference lists

**Search strategy**

- Step 1: The following databases were searched via the NHS Healthcare Databases Advanced Search (HDAS) search engines AMED, CINAHL, EMBASE, PubMed and Medline,
- Step 2: Examine the reference lists of all identified sources.

The following Boolean and free text keywords were used:

\[(1 \text{ AND } 4): \neg \text{((phenol).ti,ab AND ((pregnant*).ti,ab OR (breastfeed*).ti,ab)}\]

Evidence was also sought on using Google Scholar free text keywords.

**Results**

A database search via the NHS Healthcare Advanced Database Search (HDAS) yielded 699 articles, 87 of which appeared to be of potential relevance. After removing 46 duplicate articles, this total was reduced to 41, many of which discussed phenols other than that used in nail surgery. Further articles were found through Google Scholar and reference lists. A narrative review of the literature was then performed, with agreement on the conclusions gained from all authors.
Discussion

Phenol exposure

Although patient safety concerns have been raised for many phenols [22–25], humans are routinely exposed to such compounds environmentally as they are found in food [26,27] and are frequently used in the synthesis of cosmetics, plastics, and resins [28–32]. For the general population, cigarette smoke and smoked food products are the most common sources of phenol exposure [18]. Medical exposure to phenol occurs through the use of clinical disinfectants or during cosmetic procedures, such as chemical face peels, where multiple papers discuss phenol's systemic toxicity rather than its teratogenic effects [33–35]. Iglesias, et al. [36] evaluated the safety of phenol vapour inhalation for health care personnel while performing chemical matricectomy. They concluded that exposure to the vapour of phenol solutions of up to 95% concentration for up to 21 minutes is safe. Regarding the safety of occupational use of phenol by pregnant women, Iglesias, et al., concluded that the situation is unclear, and that further research could provide female health care workers with a better understanding of the possible risks to a developing foetus.

In 1994, the World Health Organisation calculated the "worst-case scenario" for phenol exposure of a 70kg individual working in an environment with heavily phenol-contaminated air and frequently consumes smoked food and phenol-contaminated water equivalent to 0.1mg/kg [18]. A valuable measurement to consider when calculating phenol exposure is the tolerable daily intake (TDI) which the European Food Safety Agency set in 2013 at 0.5mg/kg body weight daily [37]. It had previously been 1.5mg/kg since 1984. Workplace exposure limits (WEL) have been set in the UK to protect workers from the harmful effects of phenol. The long-term exposure limit (LTEL) is 7.8mg/m³ (8-hour time-weighted average exposure [TWA] reference period). The short-term exposure limit (STEL) for vapor is given as 16 mg/m³ (15-minute reference period) [38]. One may recall Paracelsus (of the 16th Century) clarifies that the dose makes the poison [39].

For ethical reasons, randomised controlled trials to assess maternal to foetal absorption of phenol are unavailable, so assessing data looking at phenol exposure in infants is necessary. Following a case where a 6-month-old neonate developed central nervous system depression after having treatment with Magenta (Castellani’s) paint as a treatment for seborrheic eczema, Rogers, et al., investigated a group of 16 infants, aged between 2 and 5 months, painted with the phenol-containing compound. Approximately 11-15% of the body surface was covered. In four of the children, phenol was present in their urine, resulting in the investigators ending their case series [40].

A study in France by Rolland, et al., analysed urinary phenol concentrations of repeated urine samples collected during the second and third trimesters of pregnancy among 479 pregnant women and 150 of their infants [29]. They detected multiple phenolic compounds in 90% of those tested. An earlier prospective, observational controlled study reported that miscarriage and complications during pregnancy were more common in those who are occupationally exposed to a range of organic solvents, including phenols [41]. In addition, that study noted that birth malformations were present among women who displayed symptoms associated with exposure to organic solvents, while no malformations were present in controls or those who were asymptomatic. The authors concluded from this that the risks are likely associated with dosage.

Jones-Price, et al., undertook a randomised controlled trial on CD-1 mice, assessing teratogenic concerns in phenol dosing, and found that extended periods of exposure to phenol at higher doses increased the risks of developmental malformations [42]. Again, malformations were typically noted in the offspring of dams that displayed toxicity symptoms. However, these findings were not statistically significant, and this study looked at exposure to phenol through ingestion for the mothers to phenol rather than via dermal exposure.

A separate study looking at prenatal exposure to nine different phenols present in maternal spot urine samples found that phenol exposure could be associated with adiposity, abdominal circumference, and head circumference – both positively and negatively – in the prenatal and postpartum period, up until the age of 36 months [43]. A flaw of this study was that only one spot urine sample was used, which assumes that phenol exposures would be consistent throughout pregnancy. Caution should also be exercised since the study finds positive and negative associations for different phenols in different circumstances. It is therefore difficult to draw an
accurate conclusion, from this source, about phenolic compounds and their effects on foetal/child development and to perform an accurate risk assessment for the one-off use of C₆H₅OH in podiatric applications.

Public Health England's toxicological overview states that, in oral exposure, a safe threshold for genotoxicity and mutagenicity exists due to first-pass metabolism [19], which is not the case for inhalation and dermal exposure. The American Toxicology, Substances and Diseases Registry toxicological profile found no studies reporting reproductive or developmental effects following dermal exposure or inhalation exposure [44]. However, oral exposure resulted in reproductive and developmental defects, but the phenol dosage exceeded 55mg/kg over multiple days or 667mg/kg in one day, and these studies were performed on mice and rats.

A thought experiment for risks to patient and practitioner in the use of phenol

When assessing the risks of phenol used during nail matricectomy in the pregnant mother, consideration for the total dose they receive is required. The following assumptions are made in considering the risk of toxicity for phenol use in the pregnant patient:

- Delivery of phenol is via EZ-Swabs,
- Each swab contains 0.178mg of phenol,
- Three swabs are used per sulcus (techniques vary widely and many practitioners use fewer, but a maximal phenol exposure is used for calculation),
- The applicator absorbs 100% of the phenol in each and 100% of the phenol transferred into the wound,
- No phenol is washed or wiped away during or at the end of the procedure.

Given these assumptions, the mother would receive a total dose per sulcus of 0.534mg of phenol (see Table 1), which even in a patient with a low body weight of 45kg, the dose that they would receive would be equivalent to 0.012mg/kg for a unilateral (three swab) procedure (see Table 2), a fraction of the 0.5mg/kg body weight recommended by the European Food Standards Agency [37]. For inhalation exposure, the dose of phenol used during a partial or total nail avulsion procedure per one toe is approximately equivalent to 10.1% of the STEL. Therefore, the likelihood of the pregnant healthcare worker or mother developing symptoms of toxicity from inhalation is very low, especially as the vapour would need to achieve a concentration of 7.8 or 16mg per cubic metre. These figures do not consider any phenol vaporises or become denatured by blood exposure or other materials in the procedure. Further mitigation may be achieved through mask use and disposing of swabs immediately after their removal from the surgical site, size of the room in which phenol is used and the levels of ventilation available.

<table>
<thead>
<tr>
<th>Average dose of phenol per swab</th>
<th>0.17</th>
<th>Long term exposure limit</th>
<th>7.8mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average dose of phenol per sulcus</td>
<td>0.53</td>
<td>Short term exposure limit</td>
<td>16mg</td>
</tr>
<tr>
<td>Average dose of phenol for TNA</td>
<td>0.53</td>
<td>Tolerable daily intake</td>
<td>0.5mg</td>
</tr>
</tbody>
</table>

Table 1 Phenol dosages/exposure limits.

<table>
<thead>
<tr>
<th>Procedure per toe</th>
<th>Patient weight (kg)</th>
<th>Phenol dose (mg)</th>
<th>Dose divided by weight (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral - 3 swabs</td>
<td>45</td>
<td>0.534</td>
<td>0.012</td>
</tr>
<tr>
<td>Bilateral - 6 swabs</td>
<td>45</td>
<td>1.068</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Table 2 Phenol dosages/procedure.

Metabolism of phenol and the wider consideration for developmental mutations in- and extra-utero

Studies on sheep and lambs, where most research has been performed, identified that 73% of hepatic blood flow comes directly from the umbilical vein to the foetus [45]. This blood supply is previously cleaned in the maternal circulation prior to reaching the uterus, so it is likely that the blood which ultimately reaches the foetal circulation requires minimal cleaning and that any remaining phenol would be excreted back into the maternal circulation for further decontamination. Phenol is primarily metabolised in the liver through three main processes: glucuronidation, sulfonation and oxidation. These are undertaken by the enzyme CYP2E1. CYP2E1 is found throughout the body’s tissues, including neural tissues, and it is likely that phenol is partially metabolised in the gastrointestinal tract and lungs, with the metabolites ultimately excreted via the kidneys [5,46,47]. This may mean that, within certain physiological limits, there is an acceptable threshold before maternal serum concentrations of phenol become teratogenic. However, despite partial decontamination by the maternal circulation, it is still worth considering the fetus's ability to clear phenol if it enters its circulation. García-Suastegui, et al., state that CYP2E1 is significantly implicated in various
neurologic disorders due to toxic bioactive compounds produced by its reaction with substrates [48]. Problematically for the metabolism, although fortunately with the previous information in mind, the human foetus has very low levels of CYP2E1 in utero but undergoes a rapid increase in its presence immediately after birth in the first 1-3 months with levels of CYP2E1 isoenzymes being approximately 35% of those of an adult within one year of birth [49].

With the above information in context, the forward thinking clinician may think that encouraging the pregnant patient to stimulate their CYP2E1 production would be beneficial in reducing the risk to the foetus. Behaviours such as drinking alcohol, nicotine consumption, fasting, and smoking tobacco have all been associated with a relative over-production of CYP2E1 however none of these are particularly conducive to growing a human, so looking at factors which inhibit CYP2E1 may be more helpful. It may therefore be judicious to recommend avoiding cruciferous vegetables, particularly those with isothiocyanates [50] and garlic, due to their containing diallyl sulfide [51]. Foods such as grapefruit contain furanocoumarins have frequently been recommended to be avoided for anyone taking a medication broken down along the CYP450 pathway [52]; although Vahid [53] refutes this as he found those rats on a high fat diet relatively unaffected.

Breastfeeding

There is a notable absence of literature identifying whether phenol, as used in podiatry, is likely to contaminate breast milk. A study by Henderson, et al., found no difference in the levels of phenols present in breast milk at one year compared to those on formula [54]; however, notably, the study’s demographics were made up of 89% of people with university education. This factor may be relevant, as Rolland, et al., [29] found that women who had spent less time in education had greater concentrations of phenols in their urine. Despite these points, it appears that neonates do have some ability to metabolise phenol, especially past months one to three, and this may provide a safety buffer for low levels of phenol present in a mother’s breast milk. In addition, a guideline for the public on breastfeeding babies after nail surgery by Jones [55] posits that due to the number of physiological membranes phenol has to cross, it is unlikely that phenol-contaminated breast milk will affect the baby.

Conclusion

Following calculations for the potential absorption of phenol via an EZ swab, the authors suggest that the purported risks associated with the pediatric use of phenol are overly cautious given that there is no clear association between occupational exposure to phenol and adverse pregnancy outcomes. Furthermore, although phenols are ubiquitous in the environment, these exposures have previously not been compared to those produced via phenol matricectomy. These calculations, combined with the relatively constant exposure to phenol in the environment should allow the podiatric practitioner the opportunity to offer a pregnant patient phenol nail surgery with confidence that the use of this caustic is safe for the foetus. Patient optimization may also be possible through recommending certain dietary changes in the period leading up to the procedure, however the authors would like to explicitly repeat that they do not recommend encouraging pregnant patients to smoke tobacco, drink or use nicotine products.

Future research looking at systemic phenol uptake and its relative half-life would be highly beneficial, with either blood biochemistry or urinalysis performed to identify the presence and quantity of phenol uptake for the mother and foetus and their rate of metabolism through repeat assessments at different time points. Ethical approval for such a study would, of course, be challenging; an easier first design would be to undertake urinalysis before and after nail surgery in non-pregnant females, specifically looking at the quantity of phenol and other metabolites. Similar research should also be considered for pregnant healthcare workers using phenol for medical procedures on their patients.

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