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Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [1]

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. What are benzoic acid and benzoates and why are they used as excipients?

Benzoic acid and its salts (Na or K salts) is a bacteriostatic antiseptic that is only active in an acidic environment (pH 2.5 to 4.5).

In mammals, benzoic acid is primarily metabolized to its glycine conjugate, hippuric acid, which is readily excreted via the renal organic anion transport system. Moreover, benzoic acid is also found as a metabolite of benzyl alcohol (for more information on benzyl alcohol see the dedicated questions and answers document [10]).

Benzoic acid is mainly used as preservative at levels from 0.01 to 0.2%.

2. Which medicinal products contain benzoic acid or benzoates?

Benzoic acid is rarely used as such in medicines whereas its salts (benzoates) are more commonly used. Sodium benzoate is found as excipients in some medicinal products administered orally, topically (e.g. antifungals) or injected.

Benzoic acid has a long history of use as an antifungal agent in topical therapeutic preparations such as Whitfield's ointment (benzoic acid 6% and salicylic acid 3%). Sodium benzoate is also administered intravenously and orally as an active substance to infants and children for the treatment of hyperammonaemia related to urea cycle disorders. However, such uses will not be discussed in this document (not in the scope).

3. What are the safety concerns?

The main safety concern with benzoic acid and benzoates is its ability to displace bilirubin from albumin. This is of particular concern in pre-term and full-term neonates where immaturity of metabolic enzymes [8] until 8 weeks of age, may result in an accumulation of benzoic acid. Neonatal unconjugated hyperbilirubinemia and resultant clinical jaundice affect up to 85% of newborns, usually this condition is benign. However, the displacement of bilirubin from albumin leads to hyperbilirubinaemia which may cause a serious concern of brain injury in some neonates with jaundice. Thus, acute bilirubin encephalopathy may evolve to kernicterus (bilirubin-induced brain dysfunction) if left untreated. This risk exists with oral, parenteral and also cutaneous preparations, as the cutaneous absorption of benzoic acid is significant, in particular for neonates. Moreover this threat of developing a kernicterus for neonates is also to be considered when benzyl alcohol [3, 5] is used since benzoic acid is one of its metabolites as previously mentioned. Co-administration of products containing either excipient must be used with caution in paediatrics since both share similar metabolic pathways and may accumulate.

A multigenerational study in rats using dietary administration of benzoic acid, found no effects on birth weight, postnatal growth or survival up to 750 mg/kg bw/day [7]. In a dietary study on sodium benzoate, toxicity on the foetuses and delivered offspring of Wistar rats were seen at very high doses, and a NOAEL of 1310 mg/kg bw/day was identified [9].

NOAELs from gavage administration were slightly lower than those from dietary administration. The exact mechanism of the foetal and offspring toxicity, seen at high doses in some studies, cannot be determined from the data available; it could be secondary to maternal toxicity.

However, identifying the mechanism of toxicity is not critical to the evaluation since there are adequate data to establish an overall NOAEL of 500 mg/kg bw/day [12].

According to the opinion of the Scientific Committee on Consumer Products (SCCP) in 2005 [11] the acceptable daily intake (ADI) for benzoic acid and its salts has been established to 0–5 mg/kg bw in agreement with the WHO/JECFA report of 1996 [6]. Young children (< 3 years old) may not be sufficiently mature to metabolise and eliminate benzoic acid as efficiently as adults. Therefore the upper limit of the ADI should be considered with caution in this age group [12].

4. What are the reasons for updating the information in the package leaflet?

The information for the package leaflet in the 2003 guideline (see Annex 1) needs to be further expanded regarding the risk to neonates and the route of administration.

5. Proposal for an updated information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	All routes of administration	Zero	This medicine contains x mg <benzoic acid/benzoate salt> in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	
	Oral, parenteral	Zero	<Benzoic acid/benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
	Topical	Zero	<Benzoic acid/benzoate salt> may cause local irritation.	May cause non-immunologic immediate contact reactions by a possible cholinergic mechanism.
			<Benzoic acid/benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Absorption through the immature skin of neonates is significant.

Further scientific background is available in the report entitled ‘Benzyl alcohol and benzoic acid group used as excipients’ [2].

References

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12. SCF (Scientific Committee on Food) 2002, Opinion of the Scientific Committee on Food on Benzoic acid and its salts, SCF/CS/ADD/CONS/48 Final, September 2002.

Annex 1 - Information in the package leaflet as per 2003 Guideline [4]

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzoic acid and benzoates: **for example:** **E210 benzoic acid** **E211 sodium benzoate** **E212 potassium benzoate**	Topical	Zero	Mildly irritant to the skin, eyes and mucous membranes.	
	Parenteral	Zero	May increase the risk of jaundice in newborn babies.	