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Risk assessment of topically applied products

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Abstract

The human risk of harmful substances in semisolid topical dosage forms applied topically to normal skin and broken skin, respectively, was assessed. Bisphenol A diglycidyl ether (BADGE) and three derivatives of BADGE previously quantified in aqueous cream and the UV filters 3-BC and 4-MBC were used as model compounds. Tolerable daily intake (TDI) values have been established for BADGE and derivatives. Endocrine disruption was chosen as endpoint for 3-BC and 4-MBC. Skin permeation of the model compounds was investigated in vitro using pig skin membranes. Tape stripping was applied to simulate broken skin associated with various skin disorders. BADGE and derivatives had a tendency to permeate pig skin membranes in vitro with higher fluxes in the tape stripped membranes compared to the non-treated membranes. Data from the in vitro skin permeation study and from the literature were used as input parameters for estimating the risk. The immediate human risk of BADGE and derivatives in topical dosage forms was found to be low. However, local treatment of broken skin may lead to higher exposure of BADGE and derivatives compared to application to normal skin. 3-BC permeated skin at higher flux than 4-MBC. Both UV filters are endocrine disrupting compounds with 3-BC being the more potent. UV filters in sunscreen are often present in high concentrations, which potentially may lead to high systemic exposure dosages. Thus, the risk associated with use of 3-BC and 4-MBC containing sunscreen with regards to endocrine disrupting effects was found to be high and more data is urgently needed in order to fully assess the human risk of 3-BC and 4-MBC in commercial sunscreen.

Keywords: BADGE; 3-BC; 4-MBC; Skin permeation; Tape stripping; In vitro; Flux; Extractable; Leachable; Sunscreen

1. Introduction

Psoriasis and atopic dermatitis are skin disorders characterised by an impaired barrier function (broken skin) (Choi and Maibach, 2005; Madison, 2003). These disorders are commonly treated locally by semisolid topical dosage forms (creams, gels and ointments) containing one or more drug substances, e.g. vitamin D derivatives and corticosteroids. Semisolid topical dosage forms are frequently contained in aluminium container closure systems internally coated with epoxy phenol lacquer. It has previously been shown that epoxy phenol lacquer in aluminium container closure systems may leach bisphenol diglycidyl ethers and derivatives to aqueous cream (Søeborg et al., 2006b). The toxicity of bisphenol A diglycidyl ether (BADGE) and its derivatives has previously been evaluated (Scientific Panel on Food Additives, 2004) but the potential risk of topical exposure from BADGE and derivatives also in connection with broken skin is unknown. The same epoxy phenol lacquer is used in the food industry and specific migration limits for the sum of

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BADGE and its hydrolysis and chlorinated derivatives in foods has been set. From January 2005, the use of bisphenol F diglycidyl ether was no longer permitted in the manufacture of food packaging materials in the European Union (EU) (European Commission, 2005).

As active compounds and thus intended to be present in semisolid topical dosage forms, endocrine disruptive chemical UV filters constitute another potential source of human exposure to harmful substances from semisolid topical dosage forms (Durrer et al., 2005; Kunz et al., 2006; Schlumpf et al., 2004). Commercially

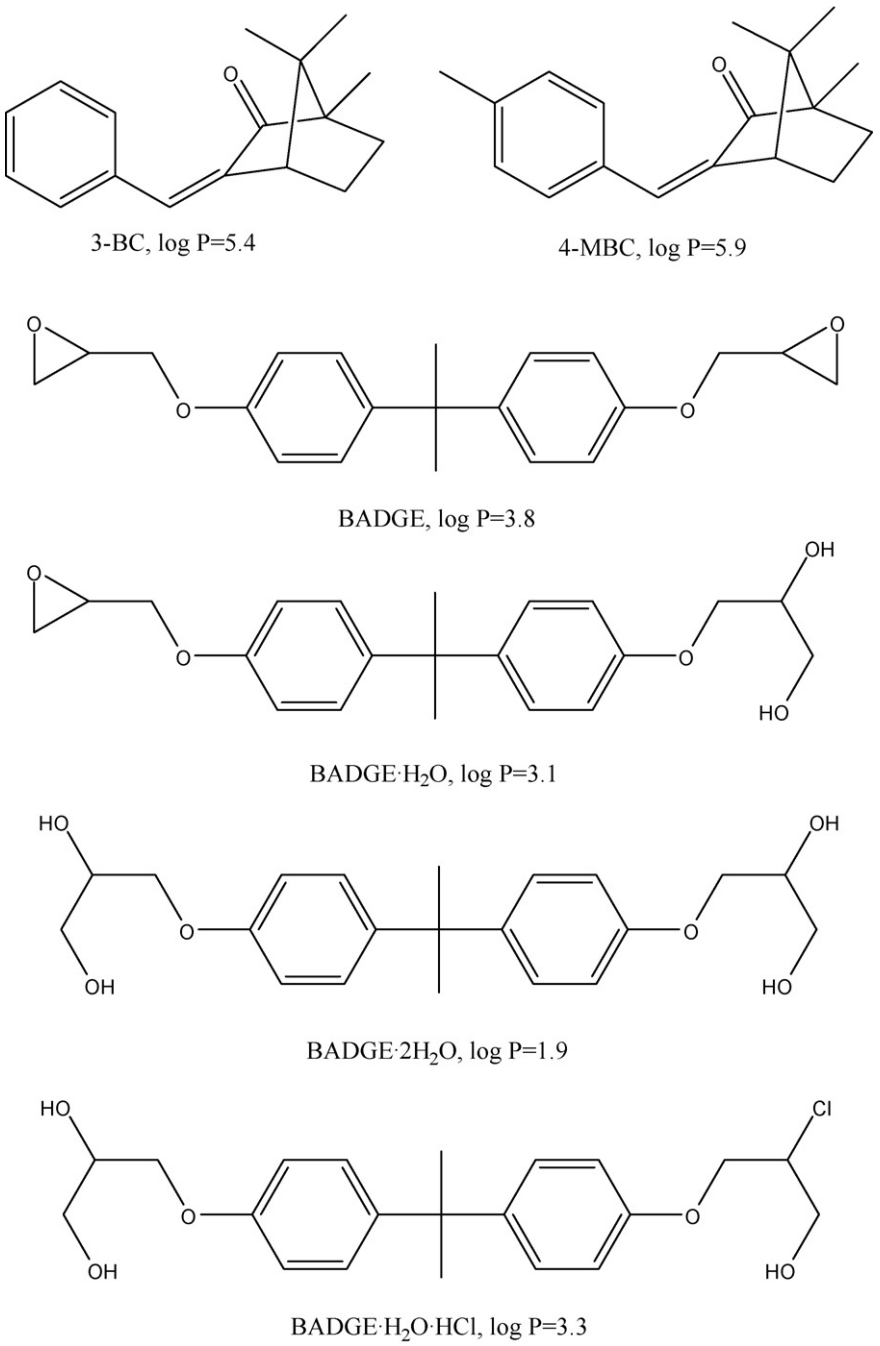

Fig. 1. Chemical structures and log *P* values of the model compounds. Log *P* values were estimated online 6 September 2006 at http://www.syrres.com/esc/est_kowdemo.html.