THE *IN VITRO* PERCUTANEOUS ABSORPTION OF RADIOLABELLED TETRABROMOBISPHENOL A (TBBPA) THROUGH HUMAN SKIN

Roper CS[1], Madden S[1], Biesemeier JA[2], McBriarty J[3] and Rothenbacher K[4]
[1]Charles River Laboratories, Tranent, Edinburgh, UK; [2]Chemtura Corporation, West Lafayette, IN, USA; [3]Ameribrom, Inc., South Charleston, WV, USA and [4]Bromine Science and Environmental Forum (BSEF), Brussels, Belgium

Abstract

Tetrabromobisphenol A (TBBPA) is a brominated flame retardant used in the manufacture of a range of domestic and consumer products. Despite the use of personal protective equipment, there remains the potential of dermal exposure to TBBPA during manufacture and packaging of the material. In order to assess the likely human health risks associated with dermal occupational exposure to TBBPA this *in vitro* study was undertaken to assess the rate and degree of absorption of [^{14}C]-TBBPA following topical application using human skin acquired from elective surgical procedures.

Following topical application of [^{14}C]-TBBPA to human split-thickness skin *in vitro*, the absorbed dose and dermal delivery were 0.73% (14.60 µg.equiv./cm^2) and 1.60% (32.05 µg.equiv./cm^2) of the applied dose, respectively. At 8 h post dose, the dislodgeable dose was 61.52% of the applied dose. At 24 h post dose, a further 28.01% was dislodged from the skin. Therefore, the total dislodgeable dose was 89.53% of the applied dose. The stratum corneum contained a further 12.48% of the applied dose. The bulk of this (9.47%) was recovered in the first 5 tape strips. Since the bulk of the stratum corneum associated material was found in the first 5 tapes strips, this indicated that the [^{14}C]-TBBPA was on the surface of the skin and that the stratum corneum was an efficient barrier to [^{14}C]-TBBPA penetration.

Introduction

Brominated flame retardants are widely used in the manufacture of a broad range of domestic and consumer products in order to reduce the potential flammability risk. Tetrabromobisphenol A (CAS No. 77-94-7), also known as TBBPA, is mainly used as a reactive flame retardant in printed circuit boards and to a minor extent as an additive flame retardant in thermoplastic polymers such as Acrylonitrile butadiene styrene (ABS). Commercial grade TBBPA contains 99.2% Tetrabromobisphenol A. TBBPA is undergoing a risk assessment by the European Union within the frame of the EU Existing Substance Regulation (Regulation 793/93), which is scheduled to be finalized in June 2007.

Despite the use of personal protective equipment, the risk of dermal exposure to TBBPA does remain, both during the manufacture of the material and packaging of the final product. In order to assist the EU risk assessment of likely human health risks associated with such occupational exposure to TBBPA this *in vitro* study was undertaken to assess the rate and degree of absorption of [^{14}C]-TBBPA following topical application using human skin acquired from elective surgery procedures.

Materials and Methods

Human skin for use on this study was obtained from patients undergoing routine elective surgery at the Plastic Surgery Unit, St John's NHS Trust (Livingston, UK). Written, informed consent was obtained from all donors. Split-thickness skin membranes were prepared from the skin samples and were mounted into flow-through diffusion cells (Scott/Dick, University of Newcastle, UK). The skin surface temperature was maintained at *ca* 32°C throughout the experimental procedure. Receptor fluid (tissue culture medium containing bovine serum albumin, glucose, streptomycin and penicillin G) was pumped underneath the skin at a flow rate of *ca* 1.5 mL/h and a tritiated water barrier integrity test performed. All skin samples with a tritiated water permeability coefficient (k_p) less than 2.5 x 10^{-3} cm/h were accepted for use.

Analysis of the [^{14}C]-TBBPA by HPLC with on-line radiodetection determined the radiochemical purity to be *ca* 99.6.

[^{14}C]-TBBPA was applied to the split-thickness human skin as a solution using acetone as the vehicle at the target application rate (*ca* 6.4 µL/cm^2, 2.0 mg TBBPA/cm^2). The acetone evaporated rapidly from the skin surface leaving behind the [^{14}C]-TBBPA. A total of 10 skin samples from 6 donors were dosed with [^{14}C]-TBBPA.

Following application of [^{14}C]-TBBPA absorption was assessed by collecting receptor fluid in hourly fractions from 0-8 h post dose (to replicate a typical period of operator exposure) at the end of which the skin surface was washed with a concentrated soap solution, cleansed with Q-Tips and dried with a tissue swab. The material washed from the skin (together with the Q-Tips) and the tissue swabs were retained for analysis by liquid scintillation counting. Following the washing procedure the absorption of [^{14}C]-TBBPA continued to be monitored by collecting receptor fluid in 2-hourly fractions until 24 h post dose. At 24 h post dose, the receptor fluid flow was stopped and the collection terminated. The skin was again dried with a tissue swab and the following terminal samples retained for analysis: receptor and donor chamber rinses, exposed and unexposed skin and the stratum corneum which was removed by successive tape stripping. All samples were analyzed by liquid scintillation counting.

The definitions have been used from OECD Guideline for Testing of Chemicals, Guideline 428: Skin Absorption: *In vitro* Method (2004).

Results and Discussion

A summary of the results is provided in the table below.

	TBBPA in Acetone
Target TBBPA Application Rate (mg/cm^2)	1.9
Actual TBBPA Application Rate (mg/cm^2)	2.0
Dislodgeable Dose 8 h (µg equiv./cm^2)	1232.47
Total Dislodgeable Dose (µg equiv./cm^2)	1793.56
Unabsorbed Dose (µg equiv./cm^2)	2048.46
Absorbed Dose (µg equiv./cm^2)	14.60
Dermal Delivery (µg equiv./cm^2)	32.05
Mass Balance (µg equiv./cm^2)	2080.52
Dislodgeable Dose 8 h (% Applied Dose)	61.52
Total Dislodgeable Dose (% Applied Dose)	89.53
Unabsorbed Dose (% Applied Dose)	102.26
Absorbed Dose (% Applied Dose)	0.73
Dermal Delivery (% Applied Dose)	1.60
Mass Balance (% Applied Dose)	103.86

Following topical application of [^{14}C]-TBBPA to human split-thickness skin *in vitro*, the absorbed dose and dermal delivery were 0.73% (14.60 µg.equiv./cm^2) and 1.60% (32.05 µg.equiv./cm^2) of the applied dose, respectively. At 8 h post dose, the dislodgeable dose was 61.52% of the applied dose. At 24 h post dose, a further 28.01% was dislodged from the skin. Therefore, the total dislodgeable dose was 89.53% of the applied dose. The stratum corneum contained a further 12.48% of the applied dose. The bulk of this (9.47%) was recovered in the first 5 tape strips. Since the bulk of the stratum corneum associated material was found in the first 5 tapes strips, this indicated that the [^{14}C]-TBBPA was on the surface of the skin and that the stratum corneum was an efficient barrier to [^{14}C]-TBBPA penetration.

Acknowledgements

This work was funded through the American Chemistry Council – Brominated Flame Retardant Industry Panel.