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Organophosphate esters’ skin penetration

Hours

TCEP & TCIPP [ng/cm²]

0 24 48 72

0 100 200 300

TDCIPP & TPHP [ng/cm²]

0 10 20 30

TCEP

TCIPP

TDCIPP

TPHP

0 24 48 72

Hours
Dermal uptake and percutaneous penetration of organophosphate esters in a human skin ex vivo model

Marie Frederiksen a,b, Heather M. Stapleton c, Katrin Vorkamp d, Thomas F. Webster e, Niels Martin Jensen f, Jens Ahm Sørensen f, Flemming Nielsen g, Lisbeth E. Knudsen h, Lars S. Sørensen a,1, Per Axel Clausen b, and Jesper B. Nielsen g.

Department of Civil Engineering, Technical University of Denmark, Brovej, 2800 Kgs. Lyngby
Abstract

Organophosphate esters (OPEs) are used as flame retardants, plasticizers, and as hydraulic fluids. They are present in indoor environments in high concentrations compared with other flame retardants, and human exposure is ubiquitous. In this study we provide data for estimating dermal uptake for eight OPEs and ranking in OPEs risk assessment. Dermal uptake and percutaneous penetration of the OPEs were studied in a Franz diffusion cell system using human skin dosed with a mixture of OPEs in an ethanol:toluene (4:1) solution. Large variation in penetration profiles was observed between the OPEs. The chlorinated OPEs tris(2-chloroisopropyl) phosphate (TCIPP), and in particular tris(2-chloroethyl) phosphate (TCEP), penetrated the skin quite rapidly while tris(1,3-dichlor-2-propyl) phosphate (TDCIPP) and triphenyl phosphate (TPHP) tended to build up in the skin tissue and only smaller amounts permeated through the skin. For tris(isobutyl) phosphate (TIBP), tris(n-butyl) phosphate (TNBP), and tris(methylphenyl) phosphate (TMPP) the mass balance was not stable over time indicating possible degradation during the experimental period of 72 hours. The rates at which OPEs permeated through the skin decreased in the order TCEP > TCIPP > TBOEP > TIBP > TNBP > TDCIPP > TPHP > TMPP. Generally, the permeation coefficient, $k_p$, decreased with increasing log $K_{ow}$, whereas lag time and skin deposition increased with log $K_{ow}$. The present data indicate that dermal uptake is a non-negligible human exposure pathway for the majority of the studied OPEs.
Keywords: PFR, OPFR, OPE, flame retardants, plasticizers, human exposure

1. Introduction

Organophosphate esters (OPEs) have been used as flame retardants, plasticizers, and in some cases also in hydraulic fluids over the past decades (ATSDR, 1997; EFRA, 2017b, a). The halting of production of polybrominated diphenyl ethers has potentially further increased the use of OPEs as flame retardants (Cooper et al., 2016). The group of OPEs comprises numerous compounds with many different types of chains on the phosphate core, some have halogenated side chains to increase their flame retardant properties, while others have pure alkyl or aryl side chains (van der Veen and de Boer, 2012); the compounds and abbreviations used are listed in Table 1 and details of suppliers in Table S1. OPEs are suspected to cause a variety of health effects. For example, three chlorinated OPEs (TCEP, TCIPP and TDCIPP) are restricted from use in toys for small children in the EU due to their carcinogenic effects (EU, 2014). In addition, emerging data suggest that OPEs are potent endocrine disruptors, affecting the thyroid hormone system, as were flame retardants they replaced (Hoffman et al., 2017; Preston et al., 2017). Some studies suggest an association between OPEs and asthma in children, though findings to the contrary exist as well (Araki et al., 2014; Canbaz et al., 2016).

OPEs are used in large quantities in consumer products including foam products and building materials such as insulation and flooring materials (Kemmlein et al., 2003; Stapleton et al., 2009; Sørensen, 2014; Hoffman et al., 2015a). The wide use of OPEs in products for indoor use has led to high levels in indoor environments (Carlsson et al., 1997; Fan et al., 2014; Brommer and Harrad, 2015; Hoffman et al., 2015b). Furthermore, the application of TNBP and TMPP in hydraulic fluids used in e.g. aircrafts, has been shown to cause significant occupational exposure (Solbu et al., 2011). OPEs in consumer products like furniture and electronics can also result in occupational exposure during production and recycling (Mäkinen et al., 2009).
Finally, some OPEs are used as plasticizers in personal care products and cosmetics such as nail polish (Mendelsohn et al., 2016) resulting in direct application to the body.

Non-occupational exposure to OPEs indoors occurs via dust ingestion, which is believed to be a major route of exposure for many brominated flame retardants (BFRs) (Wu et al., 2007; Frederiksen et al., 2009; Frederiksen et al., 2010). But in contrast to most BFRs, some OPEs have vapor pressures that result in air being a significant route of exposure too (Cequier et al., 2014; Schreder et al., 2016). Finally, dermal absorption after contact with OPE-containing materials or dust, directly applied personal care products or deposition of OPEs from air into skin oils may be other possible routes of exposure. Recently, several studies have addressed the dermal loading of OPEs using hand wipes (e.g. Stapleton et al., 2014; Liu et al., 2017; Sugeng et al., 2017). These have demonstrated that OPEs are ubiquitously found in hand wipes, proving that continuous dermal exposure to OPEs occurs.

In order to cross the skin barrier and reach circulation, a compound has to cross several skin layers; the two most important ones for dermal uptake are dermis and epidermis. Epidermis is usually the main barrier – particularly the layer of dead skin cells at the surface of the skin (stratum corneum). While dermis is hydrophilic, epidermis is lipophilic. Thus, compounds with both hydrophilic as well as lipophilic characteristics (-2 < log $K_{ow}$ < 2) have an easier passage (Nielsen et al., 2009), whereas the permeation coefficient is expected to decrease at higher as well as lower log $K_{ow}$ values. Therefore, we hypothesize that the OPEs of this study have higher permeability coefficients than previously tested extremely lipophilic novel halogenated flame retardants (Frederiksen et al., 2016). The aim of this study is to provide data for estimating dermal uptake of eight OPEs and for ranking OPEs in risk assessments.
2. Materials and Methods

2.1. Experimental dermal uptake model

Dermal uptake and percutaneous penetration were studied in a Franz diffusion cell system as previously described for brominated and chlorinated flame retardants (Frederiksen et al., 2016). In brief, skin patches from plastic surgery were used (three female donors: age 42-50 y; abdominal region; average skin thickness of 0.99 mm). The skin was mounted in Franz diffusion cells with an average exposed skin area of 2.64 cm$^2$ and 16.6 mL average volume of the receptor chamber. The receptor fluid consisted of an aqueous solution of 0.9% NaCl, 5% bovine serum albumin, 40 mg L$^{-1}$ hexamycin and Na$_2$HPO$_4$ buffer (to pH 7.4). The diffusion cells were kept in a water bath at 32°C for 24 h prior to loading. The OPEs (Table 1) were dosed in 500 µL ethanol (with 20% toluene residue) covering the entire skin surface. The use of ethanol and toluene was a compromise between solubility of the test compounds and the potential delipidization of the skin. The OPE mixture contained 1000 ng of each compound (except TBOEP where 10000 ng was added) (Table S1). Concentrations were chosen to enable detection in the receptor fluid of 1% of the loaded dose. Finally, vanillin was added as a positive control (see QA/QC section). The donor chambers were covered with parafilm to limit evaporation. In parallel, the same volume was spiked to laboratory vials (three replicates) to measure initial conditions. The water baths were covered with aluminum foil throughout the experiment to limit potential UV degradation.

The diffusion cells were taken down at three time points: 24 h (n=3), 48 h (n=5) and 72 h (n=4). From each cell the following compartments were sampled: donor cell wash, epidermis, dermis and receptor fluid as previously described in detail in Frederiksen et al. (2016). In brief, the residue in the donor chamber was collected using cotton swabs, then the skin and donor chamber was gently washed twice with ethyl acetate soaked cotton swabs, and finally the skin was dried with cotton swabs, all swabs were collectively analyzed as remains in the donor chamber. Afterwards isotonic saline was again added and the capacitance measured to ensure continued barrier integrity. The saline was removed and the cells were dismounted;
the upper skin layer (epidermis) was easily scraped off of the remaining skin fraction (dermis) using a scalpel. Finally, the entire volume of receptor fluid was sampled, and the chamber was rinsed with approximately 1 mL of fresh receptor fluid. The samples were stored at -20 °C until analysis.

The flux and permeability coefficient, $k_p$, was determined using the steepest part of the penetration curve with the maximum apparent flux (see eq. 1 and 2 of supporting information). Furthermore, $k_{p,R+S}$, including dermis and the absorbed amount, was calculated (Eq. S3 and S4). This is similar to the method previously described in Frederiksen et al. (2016).

2.2. Chemical analyses

The OPEs were analyzed at Duke University and included TCEP, TCIPP, TDCIPP, TPHP, TBOEP, and TNBP for which analytical standards were available in house (Table S1). In addition, identification of TIBP and TMPP were obtained using published information on ions and relative retention times (van den Eede et al., 2011) and comparison with initial spikes. TIBP and TMPP were quantified using dTNBP and $^{13}$C-TPHP as internal standards and the linear calibration curves of TNBP and TPHP, respectively. Thus, the quantification of TIBP and TMPP is less accurate and precise, but in most of the data analysis only relative concentrations were used (see section 3.1.), which equals relative areas.

Prior to extraction all samples were spiked with the internal standards dTNBP, $^{13}$C-TPHP, and dTDCIPP. The extraction and clean-up methods varied slightly with the matrix. The samples of donor chamber wash and epidermis were extracted by adding 10 mL ethyl acetate and sonicated for 15 min; the supernatant was transferred to a centrifuge tube and sonication was repeated twice with fresh solvent. The extracts were concentrated to approximately 0.5 mL using a SpeedVac Concentrator (Savant SPD121P, Thermo Scientific), transferred to autosampler vials and dTCEP was added to measure recovery of the internal standards. As dermis samples required further clean-up, they were extracted as described above, evaporated to 1 mL and cleaned on hand-packed Florisil columns (8 g) eluted with 50 mL ethyl acetate:acetone (1:1). The extracts were concentrated to approx. 1 mL, transferred to autosampler vials and dTCEP was added. For the
extraction of the receptor fluid an aliquot of 10 mL was spiked with internal standards, 10 mL ethyl acetate was added, and the mixture was vortexed for 1 min and centrifuged for 5 min at 3000 RPM. The extraction procedure was repeated twice with fresh solvent. The rest of the procedure was identical to the other matrices. All extracts were analyzed by GC-MS using EI (5975C/7890A, Agilent Technologies) as previously described (Stapleton et al., 2009). The positive controls were analyzed by the method used by Holmgaard et al. (2012) with minor modifications as described in the supporting information.

2.3. QA/QC

The integrity of the skin barrier was checked before and after the experiment by measuring the capacitance (Lutron DM-9023, Acer AB, Sweden). If the skin integrity was compromised, the capacitance would reveal this immediately by a marked increase above the expected capacitance of 30-80 nF. For this reason, cells with a capacitance above 100 nF at any point were excluded. We used vanillin (4-hydroxy-3-methoxybenzaldehyde) as a positive control, for which linear penetration was expected until ΔC approach zero. Vanillin was chosen as a substitute for benzoic acid, which had been used previously (Nielsen et al., 2009; Nielsen, 2010), to avoid pH changes which may affect the test compounds. The positive controls were analyzed in 1ml subsamples taken from the receptor chamber at 2, 6, 24, 48, and 72 h. The compliance between the two was tested in three cells. Results of the positive controls can be seen in Figure S1; good agreement between benzoic acid and vanillin was observed. Three Franz cells were reserved for blank cells, i.e. pure solvent was added, and run in parallel with the test cells. The blank cells were split into the four compartments just as the test cells.

The recoveries of the internal standards were on average 76-108% while 59-93% of the OPEs were recovered compared with the initial conditions (Table S2). Table S2 also shows the measured mass in the initial spikes compared with the apparent spike of 1000ng. The actual spikes were only 48-79% of the expected amount. The reason for this is not clear, but it may be due to adhesion to the glass containing the
stock solution, the pipettes and/or the glass containers used for subsequent storage. As a consequence, all comparisons are made to the measured values of the initial spikes.

The method detection limits were calculated using a signal to noise ratio of 10; if the compounds were present in blanks three times the standard deviation of the blank levels was used. Blank levels of TNBP (up to 9% of total measured) and TCIPP (up to 3% of total measured) were detected particularly in the receptor fluid; therefore matrix-specific blank corrections were made for these two compounds by subtracting the mean blank of receptor fluid or the mean of other matrices, respectively.

3. Results

The positive control substances showed that the system was stable and working well and without leaks (e.g. damaged skin) (Figure S1). The two positive controls exhibited the characteristic penetration curve with lag time, maximum flux and a leveling-off of the penetration rate at time periods extending beyond 48 hours (Figure S1).

3.1. Dermal uptake and penetration profiles

A large variety of penetration profiles was observed for the OPEs. The chlorinated OPEs, TCIPP and in particular TCEP, penetrated the skin quite rapidly and the diffusion to the receptor fluid was fast, resulting in a marked accumulation in the receptor chamber and reduction in the donor chamber within the study period. For TCEP, an initial small build-up in the skin was also depleted before the termination of the experiment (Figure 1). Likewise, TDCIPP and TPHP decreased markedly in the donor chamber during the experiments, but these compounds tended to accumulate in the skin tissue, primarily in the upper layers, and only smaller amounts reached the receptor fluid within the experimental period of 72h.

Taking the cells down at different time points rather than sampling repeatedly, allowed us to examine the time dependency of the total measured mass. This showed that for the four compounds mentioned above the total measured mass was stable over time. However, a continuous mass loss was observed for TNBP,
TIBP and TMPP over time (Figure S2); the possible reasons for this are discussed further in section 4. Consequently, the results for these three compounds are given as a percentage of the total recovered mass in each individual cell as shown in Figure 2. Due to significant uncertainty of TBOEP-quantification, TBOEP was added to this group and treated accordingly (Figure 2). In the following TNBP, TIBP, TBOEP and TMPP are referred to as semiQ-OPEs. The results of the semiQ-OPEs showed that uptake was slower than for TCEP (Figure 2). TMPP was not detected in the receptor fluid above LOQ even after 72h although accumulation in the skin was observed.

3.2. Flux and permeability coefficient

Maximum apparent flux and permeability coefficients, $k_p$, were estimated (Table 2) from the amounts found in the receptor fluid using the steepest part of the curve (selected range used in the calculation can be found in Table S3). The $k_p$ can be used for ranking the compounds, thus the rate at which the OPEs penetrate the skin decreases in the following order TCEP > TCIPP ≥ TBOEP > TIBP ≥ TNBP > TDCIPP > TPHP > TMPP (compounds in italics are semi-quantitative). Generally, the $k_p$-values were found to decrease with increasing $\log K_{ow}$ (Figure S3). Furthermore, skin deposition (dermis+epidermis) and lag time tended to increase with increasing $\log K_{ow}$ (Figure 3).

4. Discussion

4.1. Dermal uptake and percutaneous penetration

For the present selection of OPEs, we expected the highest penetration rate for TCEP, the OPE with the lowest $\log K_{ow}$ (1.66), and decreasing penetration rates and thereby $k_p$ values for the other OPEs that have increasing $\log K_{ow}$ values (up to 6.34). The observed penetration profiles were similar to those previously reported for the chlorinated OPEs with TCEP having a shorter lag-time and penetrating faster than TCIPP and TDCIPP (Abdallah et al., 2016). A study using mouse skin found that a considerable amount of TDCIPP was absorbed into the receptor fluid (Hughes et al., 2001), but mouse skin is generally more permeable than human skin (Ghosh et al., 2000); no other OPEs were included in that study. In the current study we
found that while the percutaneous penetration decreases with increasing lipophilicity the skin deposition increases. This is consistent with previous findings for other compounds, including organophosphate pesticides (Nielsen et al., 2009). It is likely due to the dermis becoming an increasingly important barrier for the diffusion and thus a (at least temporary) build-up is occurring. This underlines the importance of considering both epidermis and dermis in the description of dermal uptake and percutaneous penetration of lipophilic compounds (Nielsen et al., 2004). For compounds with a fast diffusion rate, the donor chamber depletes during the experiment and decreasing levels in the skin may be observed, as in the case of TCEP in the current study. Another important point is that in in vitro and ex vivo studies without ongoing circulation through the dermis, ignoring the deposition in especially the dermis may cause an underestimation of the potential in vivo absorption. In the current study, the amount retained in dermis was measured, for TDCIPP, TPHP, TIBP and TNBP inclusion of dermis in the calculation of flux and $k_p$ resulted in higher values. For TMPP the increase was marginal as only notable levels were found in the epidermis (Table 2).

We have previously reported decreasing $k_p$ with increasing log $K_{ow}$ for highly lipophilic halogenated flame retardants (log $K_{ow}$ 6.34-13.6, EpiSuite v. 4.11). The OPEs penetrated the skin both faster and to a greater extent than we had previously observed for highly lipophilic brominated and chlorinated flame retardants (Frederiksen et al., 2016), in accordance with our expectations based on their physical-chemical properties i.e. primarily there lipophilicity. The compounds in this study had lower log $K_{ow}$-values (1.66-6.34), nevertheless the same trend was observed (Figure S3). So even for these OPEs diffusion across dermis seems to be the rate limiting step of the penetration at least ex vivo.

The somewhat crude time resolution of the samplings in the current study may lead to underestimation of the lag time. However, since the amount of all OPEs were very low even at 24h the underestimation is expected to be limited. Likewise, crude time resolution may lead to underestimation of flux as well as $k_p$, but only TCEP (and to some degree TIBP) show a decrease in the flux towards the end of the experiment, thus the underestimation is expected to be limited for the majority of compounds. Furthermore, absolute
values of $k_p$ generally depend on the specific setup; however, an inter-laboratory study has shown that
even when absolute $k_p$-values of test compounds differ between laboratories the rank order is almost
identical across laboratories (van de Sandt et al., 2004), thus rank orders are more generalizable than actual
values. We also observed that the rank order was unaffected by inclusion of dermis in the $k_p$ estimate. The
$k_p$s obtained in the current study were lower but within one order of magnitude of those reported by
Abdallah et al. (2016) and more importantly the same rank order was observed for the compounds that
both studies had in common.

4.2. Mass loss

The overall recovery of TCEP, TCIPP, TDCIPP and TPHP were 59-93% compared to the initial spike and with
large variation. This could possibly be due to adherence to surfaces of the Franz cells or other equipment
used in the experiment. Unfortunately, this was not tested during the experiment. For halogenated flame
retardants, adherence was not a problem in the same system (Frederiksen et al., 2016). Marek et al. (2017)
reported that adherence of n-phenyl-2-naphtylamine (log $K_{ow}$ of 4.4) was highly dependent on the receptor
fluid; adding 5% bovine serum albumin to the receptor fluid, as it was done in the current study, markedly
reduced the adherence to the glass surfaces in the receptor chamber.

The observed loss of mass of TNBP, TIBP and TMPP during the experiment naturally leads to larger
uncertainties related to the results of the semiQ-OPE, as we cannot argue that the relative loss in recovery
is equally distributed between compartments, nor that it is lost from only one compartment, e.g. the
donor. Since all compounds were added at the same time to the same cells methodological issues can be
ruled out as a possible explanation as both the positive controls and the majority of OPEs are stable. We
had limited the evaporation by covering the cells with parafilm and the UV-degradation by covering the
stainless steel water bath with aluminum foil during the entire experimental period. We suspect that
degradation could have taken place for example by hydrolysis of TNBP, TIBP and TMPP. Su et al. (2016)
found that OPEs’ resistance to base-catalyzed hydrolysis depends on the side chains; resistance to
degradation decreases in the order aryl > chlorinated alkyl > alkyl side chains. One notable exception is TMPP that Su et al. (2016) found to degrade more easily than TPHP. Both the general pattern and the exception of TMPP fit well with the stability patterns we observed (Figure S2). OPE-hydrolysis can also be acid-catalyzed (US.EPA, 2006), but no difference in degradation could be observed in the three cells where benzoic acid was used as positive control. For the compounds included in this study, Su et al. (2016) found that the degradation was only significant within a few days at extreme pH-conditions at 20 °C; however, our experiments were performed at 32 °C, which would accelerate the process considerably. Finally, the possibility of remaining active esterases in the skin even after prolonged storage at -20 °C cannot be ruled out.

As correction to total mass may overestimate the flux and permeability of the semiQ-OPE we chose to report values of flux and permeability conservatively not correcting for mass loss (Table 2); however, the two estimates are actually quite close (Table 2 and Table S4).

4.3. Implications for exposure

Studies of hand wipes have shown ubiquitous dermal exposure to OPEs (e.g. Stapleton et al., 2014; Liu et al., 2017; Sugeng et al., 2017). Our results indicate that the presence of some OPEs on the skin e.g. TCEP would lead to greater concern about uptake than for other compounds e.g. TMPP. Nevertheless, despite our result showing that the skin is less permeable to TPHP than most of the other studied OPEs, Mendelsohn et al. (2016) showed that application of nail polish with TPHP resulted in significant dermal absorption and urine excretion, though in this case dermal absorption it likely to occur through the cuticles where the distance for diffusion is much shorter than for full thickness skin. A few studies have included both hand wipes and urines samples finding significant correlations for TDCIPP, TCIPP and TPHP (Hoffman et al., 2015b; Hammel et al., 2016). Further, an inverse effect of hand washing frequency on levels of urinary metabolites of OPEs has been observed (Carignan et al., 2013). Generally, predominant compounds in hand wipes result in their metabolites being predominant in urine (e.g. Hoffman et al. (2015b)). This may
conflict with the observation that OPEs are dermally absorbed at very different rates. However, real world exposures may be chronic and combine both dermal and other correlated routes of exposure such as hand-to-mouth contact that would also be reflected in urine samples.

In the current study, the compounds were added on the skin in solution. This differs significantly from real world conditions, but if the compounds are bioavailable the observed rank order should still apply. For example, if OPEs are absorbed from air into skin oils as suggested for other SVOCs by Weschler and Nazaroff (2014) it may be very similar to the current situation. On the other hand, if the majority of exposure is via contact with dust or materials, diffusion across the boundary layer or within materials may become the rate-limiting step (Clausen et al., 2016). However, studies including hand wipes, dust, air and wrist bands indicate that the correlation may be stronger between hand wipes and air than between hand wipes and dust (Stapleton et al., 2014; Hoffman et al., 2015b; Hammel et al., 2016; Xu et al., 2016).

The current study has shown that OPEs can be absorbed dermally, some compounds fairly easily. These findings should be taken into consideration when planning the use of flame retardants in products.

5. Conclusion

In the current study, the dermal uptake and percutaneous penetration of eight OPEs were explored. The obtained permeability coefficients are valuable for ranking compounds in risk assessments. In line with our previous study on highly lipophilic halogenated flame retardants, the studied OPEs showed a decreasing trend of penetration rates with increasing log $K_{ow}$. For the more lipophilic compounds the largest fraction was accumulated in the skin. Many OPEs are found at high levels in indoor environments; and combined with the present data it is clear that dermal uptake is a non-negligible exposure pathway for the majority of the studied OPEs.

6. Acknowledgements

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7. References


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### Table 1. Acronyms, abbreviations and CAS numbers for the OPEs in the study.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Name</th>
<th>CAS</th>
<th>Log $K_{ow}$</th>
<th>MW</th>
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<tr>
<td>TCEP</td>
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<td>Tris(2-chloroisopropyl) phosphate (mixture of isomers)</td>
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<tr>
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<td>Tris(methylphenyl) phosphate (technical mixture of isomers)</td>
<td>1330-78-5</td>
<td>6.34</td>
<td>368.4</td>
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</table>

*estimated using EpiSuite v. 4.11

### Table 2. Apparent flux and permeability coefficients of OPEs. Conservative estimates for semiQ-OPEs (in italics) are provided, not corrected for mass loss.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Flux [ng cm$^{-2}$ h$^{-1}$] (Absorption = receptor only)</th>
<th>$k_p$ [10$^{-4}$ cm h$^{-1}$] (Absorption = receptor only)</th>
<th>$k_{p,R+S}$ [10$^{-4}$ cm h$^{-1}$] (Absorption = receptor+dermis)</th>
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<td>5</td>
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<td>TBOEP</td>
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</tbody>
</table>
Figures, Frederiksen et al.

Figure 1. OPEs in different compartments of the Franz diffusion cell system as a function of time (mean and the standard error of the mean, SEM).
Figure 2. Percent of total measured mass of the semiQ-OPEs in different compartments of the Franz diffusion cell system (mean and SEM). At t₀ the OPE mass in the donor compartment is set to 100%.
Figure 3. a) OPEs in skin at 72 h, percent of applied dose (n=3, mean and SEM) and b) lag time as a function of log $K_{ow}$. TMPP lag time is set to 72h. Open symbols are semiQ-OPEs; triangles in b) are the positive controls.
Highlights

- Dermal uptake of organophosphate esters (OPEs) were determined
- TCEP is transported fastest of the studied OPEs across the skin
- Dermal uptake decreased with increasing log $K_{ow}$
- Skin deposition increased with increasing log $K_{ow}$
- Dermal absorption is an important exposure pathway for OPEs