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A Reevaluation of Methods for Assessing Dermal Exposure

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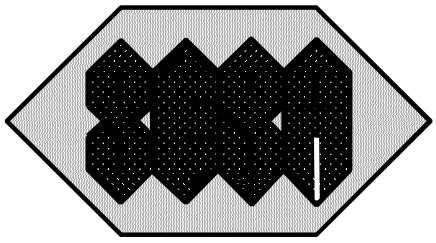

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PREFACE

Under purchase order 43-57G3-3-C5374 from USDA/APHIS, SERA (1993) prepared a review and evaluation of methods used to estimate exposure to pesticides. The report, *Special Issues Related to the Assessment of Pesticide Absorption*, includes methods for estimating dermal absorption rates, the uptake of pesticides from contaminated vegetation, and worker exposure involving the application of pesticides. The analysis of dermal absorption rates and the uptake from contaminated vegetation are published in the open literature (Durkin et al. 1995). The analysis of worker exposure is not published in the open literature but is used by the Forest Service to conduct human health risk assessments under the current contract.

The following paper presents a reanalysis of the dermal absorption data that is suitable for publication. Additional details of the analyses that would be too voluminous for a typical publication are included as part of the report submitted under this task [SERA TR 98-21-08-01d, dated May 15, 1998]. In preparing this paper for publication, some additional analyses were conducted that are not included in the formal report.

PRE-SUBMISSION DRAFT
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A REEVALUATION OF METHODS FOR ASSESSING DERMAL ABSORPTION

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ABSTRACT

This paper re-examines an earlier analysis by the Durkin et al. (1995) on the different types of dermal exposure scenarios that may be characterized by either first-order or zero-order (Fick's first law) absorption models. In addition, this paper presents a substantial expansion and analysis of a unique and highly relevant series of studies by Feldmann and Maibach (1969, 1970, and 1974) that may be used to estimate first-order dermal absorption rate coefficients. The reanalysis of the Feldmann and Maibach data is based on estimated absorption rate coefficients rather than simple observed absorption rates, as well as a much less arbitrary censoring of the data compared to the earlier analysis by Durkin et al. (1995). In addition, the equations that describe the relationship of the absorption rate coefficients to physicochemical properties (Equations 12 and 13) are qualitatively similar to the equations recommended by U.S. EPA (1992) in the estimation of dermal permeability. While the underlying processes involved in dermal absorption are likely to be zero-order in cases where the individual is effectively immersed in a large volume of contaminated fluid, the present analysis suggests that 'dry deposition' scenarios are likely to be better modelled using the assumption of first-order dermal absorption. For highly lipophilic compound, nonetheless, the differences between these two methods when applied to comparable exposure scenarios is, in general, not likely to be substantial. For more lipophilic compounds, however, the differences will be substantial.

INTRODUCTION

Dermal absorption may be an important route of exposure in several exposure scenarios for workers and the general public. Because many estimates of safe or at least tolerable doses (e.g., RfDs or MRLs) are expressed in units of mg/kg/day and based on oral toxicity studies but very few exposure criteria are based on dermal toxicity studies, risk assessments often attempt to convert dermal exposure data to units of mg/kg/day absorbed dose. For some types of dermal exposures involving direct and continuous contact with liquids, Fick's first law (zero-order absorption) may be applied in which dermal permeability (K_p in units of cm/h) is used as the index of dermal absorption. In other cases, such as those involving spills onto the skin surface or dermal exposure to contaminated vegetation, Fick's first law is less clearly applicable.

The U.S. EPA (1992) has detailed the literature relating to and guidelines for the application of Fick's first law and has suggested methods for estimating K_p in the absence of direct experimental data. As an alternative approach for exposure scenarios in which zero-order absorption may be questionable, Durkin et al. (1995) have presented an analysis of a series of studies on the dermal absorption of pesticides by humans (Feldmann and Maibach 1969, 1970, and 1974) in which dermal absorption is expressed as the proportion or percent of the applied dose absorbed per unit time.

The series of studies by Feldmann and Maibach represents a unique and highly relevant source of information on *in vivo* dermal absorption in humans. As discussed in U.S. EPA (1992), however, the Feldmann and Maibach publications do not provide sufficient experimental

details for the complete derivation of zero-order dermal absorption rates. Nonetheless, as illustrated by Durkin et al. (1995), estimates of dermal absorption rates from the Feldmann and Maibach publications gave much better estimates of absorbed dose than did estimates based on Fick's first law.

This paper re-examines the approach recommended by Durkin et al. (1995). This re-examination is motivated by three major limitations in and concerns with the Durkin et al. (1995) analysis: the direct use of time specific absorption rates from Feldmann and Maibach (1969, 1970, 1974) rather than kinetic absorption coefficients, the method of data censoring used in proposing equations for estimating dermal absorption, and the inconsistencies between the equations developed by Durkin et al. (1995) and those recommended by U.S. EPA (1992).

CURRENT APPROACHES

When the critical components of the exposure can be defined by duration, exposed skin area, and concentration of the toxic agent in an aqueous solution, a common measure of dose is DA_{event}, the cumulative dose absorbed per unit area of exposed skin for each event (mg/cm^2-event). As discussed by U.S. EPA (1992), DA_{event} may be calculated based on Fick's first law:

$$DA_{(mg/cm^2\text{-}event)} = K_p \cdot C_w \cdot t_{event} \quad \textbf{(1)}$$

re:

K_p = permeability coefficient for water (c

C_w = concentration of chemical in water (m

$_{event}$ = duration of the event in hours

The absorbed dose (D), in units of mg/kg, may then by calculated from the surface area (SA) of the skin that is contaminated and body weight (BW) of the individual:

$$D_{mg/kg\ bw} = DA_{mg/cm^2\text{-}event} \cdot SA_{cm^2} \div BW_{kg} \quad \textbf{(2)}$$

For ‘neat’ exposures (i.e., chemicals not in solution) U.S. EPA (1992) recommends using the solubility of the compound in water as the estimate of C_w. A rationale for this approach when applied to deposition exposures is that ‘crystalline’ or solid forms of a chemical are not absorbed directly through the skin and the absorption process requires the dissolution of the compound into extracellular water on the skin surface. Since the amount of the compound on the skin is likely to be much greater than the amount of extracellular water on the surface of the skin, the exposure seems identical to that of a saturated aqueous solution.

For most compounds, measured values for K_p are not available. U.S. EPA (1992) recommends the following equation from Potts and Guy (1992):

$$\log K_p = -2.72 + 0.71 \log K_{o/w} - 0.0061 MW \quad \textbf{(3)}$$

where K_p is expressed in units of cm/hour. This equation is based on measured K_p values for 95 organic compounds (Flynn 1990, Table 5-4 in U.S. EPA 1992) with log $K_{o/w}$ values ranging from -2.25 to 5.49 and molecular weights ranging from approximately 30 to 770. Although not explicitly stated in the EPA report, 3 of the 93 data points are censored from the analysis because they are statistical outliers: [Hydrocortisone-21-yl]-hemipimelate, n-nonanol, and n-propanol. With this censoring, the squared correlation coefficient for the model is about 0.68. Without censoring, the squared correlation coefficient is about 0.43.

As reviewed by the U.S. EPA (1992), some analyses (e.g., Flynn 1990) suggest that the effects of both molecular weight and lipophilicity on permeability may be linear only within certain limits. Based on the analysis by Flynn (1990), relatively lipophobic compounds with log $K_{o/w}$ values < 0.5 appear to have log K_p values of approximately -3 (MW < 150) or -5 (MW > 150). At the upper limit, highly lipophilic compounds with log $K_{o/w}$ values > 3 and molecular weights < 150 appear to have log K_p values of approximately -0.5. Compounds with log $K_{o/w}$ values > 3.5 and molecular weights > 150 appear to have log K_p values of approximately -1.5 (Flynn 1990).

The above approach is recommended for estimating exposures to 'neat solutions' involving contamination of the skin surface with a fixed amount of a pesticide that does not remain in solution. Take for example an accidental spill in which most of the liquid runs off the surface of the skin while the remainder of the solvent—usually water or an organic solvent—evaporates from the skin surface within a relatively short time. This type of exposure is referred to here as *dry deposition*.

As discussed in Durkin et al. (1995), the approach based on Fick's first law (i.e., Equations 1 and 2) appears to substantially overestimate absorbed doses from dry deposition, specifically with respect to the dermal absorption of 2,4-D after dermal contact with contaminated turf. As an alternative, Durkin et al. (1995) developed an equation for estimating the percent of dose applied to or deposited on the skin that would be absorbed per unit time:

$$\log_{10}(\%_{Abs}) = -0.004 MW + 1.5 \quad \textbf{(4)}$$

where $\%_{Abs}$ is the average daily absorption expressed as the percent of applied dose and MW is the molecular weight. Equation 4 is based on the average percent absorption per day from the studies by Feldmann and Maibach (1969, 1970, and 1974).

As discussed by Durkin et al. (1995), compounds with log $K_{o/w}$ values equal to or less than 1.85 had to be censored from the analysis. With this censoring, the squared correlation

coefficient for the equation was approximately 0.66 and a p-values of < 0.00001. The explicit inclusion of $K_{o/w}$ or other physical properties did not improve the correlation.

Equation 4 may applied to scenarios such as those involving a spill on to the surface of the skin. In such scenarios, it is important to estimate the amount of liquid adhering to skin surface. Only one study (Mason and Johnson 1987) encountered in the literature specifically measures such retention. In the Mason and Johnson (1987) study, 4 mg liquid/cm^2 of skin surface was retained on hands removed immediately from beakers containing water or ethanol. The retention was measured as the difference in the amount of liquid in the beakers before and after the hands were immersed. When beakers containing light paraffin oil were used, approximately twice the amount, 8 mg liquid/cm^2 of skin surface, was retained. In most instances, using these values should result in a plausible upper estimate of retention because chemical loss from the skin surface due to moving or washing was not considered in the Mason and Johnson (1987) measurements. Thus, the amount of chemical transferred to the skin after a spill may be calculated as:

$$D_{Skin} = RF \cdot P \cdot A$$

e deposited on the surface of the skin (µg)
ention factor (µg/cm^2) (for example, 4000–8
portion of agent in the liquid
n area exposed (cm^2)

(5)

Estimates from Equation 5 may then be used with the estimated dermal absorption rate from Equation 4 to estimate the absorbed dose:

$$D_{Abs} = D_{Skin} \cdot P \cdot t \qquad \textbf{(6)}$$

where ***P***, the absorption rate, is expressed in units of proportion of applied dose per unit time (***t***).

A limitation in the Durkin et al. (1995) analysis is that the absorption rates reported in Feldmann and Maibach (1969, 1970, 1974) and used to develop the above equation are simply time specific excretion rates rather than kinetic rate coefficients. In other words, the rates are simple experimental observations rather than estimates derived from an explicit kinetic model. These reported values were used directly by Durkin et al. (1995) because Feldmann and Maibach (1969, 1970, and 1974) do not provide any kinetic analyses other than reported intravenous (i.v.) half-times. The concern with the approach taken in Durkin et al. (1995) is that the use of reported absorption rates rather than estimates of kinetic parameters - i.e., absorption rate coefficients - could obscure any underlying relationship between physicochemical properties and estimates of dermal absorption.

In developing the equation for estimating dermal absorption rates, the approach to censoring taken by Durkin et al. (1995) is also of concern because of its arbitrary nature. Censoring apparent outliers based on $K_{o/w}$ values as done by Durkin et al. (1995) is not uncommon. The equation used by the U.S. EPA to estimate K_p values has a similar limitation. Nonetheless, except for the empirical observation that the correlation appears to break down for compounds with a log K_p < 1.85, Durkin et al. (1995) had no justification for the data censoring.

Finally, Durkin et al. (1995) found that the molecular weight was the sole determinant of the dermal absorption fraction and that $K_{o/w}$ had no impact on the relationship other than as a criterion for data censoring. Conversely, the U.S. EPA (1992) has noted that K_p is best estimated as a function of both molecular weight as well as $K_{o/w}$. This inconsistency is not intuitively satisfying because both K_p values and first-order dermal absorption rates should reflect the same basic process, and it seems sensible that both should be related to similar physicochemical parameters.

METHODS

In the reevaluation of the Feldmann and Maibach (1969, 1970, 1974) studies, both zero-order and first-order absorption models were used with the first-order elimination rates reported in Feldmann and Maibach publications to derive estimates of the zero-order and first-order kinetic rate coefficients, k_a. The kinetics of zero-order and first-order absorption with first-order elimination are detailed in standard texts on pharmacology and kinetics (e.g., O'Flaherty 1981, Goldstein et al. 1974).

Zero-order absorption with first-order elimination is expressed as:

$$X_t = \frac{k_a}{k_e}(1 - e^{k_e t}) \qquad \textbf{(7)}$$

where X_t is the amount of drug in the circulation at time t, k_a is the zero-order rate coefficient in units of amount per unit time - e.g., mg/hour - and k_e is the first-order elimination rate coefficient in units of reciprocal time - e.g., hours^{-1}. Because of the manner in which data are reported in the Feldmann and Maibach publications, however, the absorption rates had to be calculated in units of proportion of absorbed dose per hour. Nonetheless, the zero-order absorption model could be applied.

Under the assumption of first-order absorption, the proportion of the applied dose (***P***) that is absorbed dose at time t can be calculated as:

$$P_{Abs} = 1 - e^{-k_a t} \qquad \textbf{(8)}$$

Standard first-order absorption with first-order elimination is expressed as:

$$X_t = \left(\frac{k_a D}{k_e - k_a} \right) (e^{-k_a t} - e^{-k_e t}) . \quad \textbf{(9)}$$

In both of the above equations, k_a is the first-order absorption rate coefficient in units reciprocal time, D is the dose - e.g., mg deposited on the skin - and the other terms are as defined above.

Equation 9, however, is not the most appropriate model for the Feldmann and Maibach studies because absorption is the only mechanism of loss from the skin surface that is incorporated into the model. In the Feldmann and Maibach studies, the treated area of the skin was not protected and the individuals were allowed to wash the surface of the treated area 24 hours after the compound was applied. Thus, losses from the skin surface due to factors other than absorption (e.g., exfoliation, abrasion, or washing) were inevitable. In this report, these losses are referred to as *fugitive losses* - i.e., any loss from the surface of the skin other than through dermal absorption.

In an attempt to explore the effect of fugitive losses, a simplifying assumption was be used in this analysis: the net rate of removal from the skin surface due to processes other than absorption can be described by a composite first-order rate coefficient, k_r. Thus, the rate of change in the amount of chemical on the skin surface at time t (dA/dt) is determined by the amount of chemical remaining on the skin at time t, the absorption rate (k_a), and the rate of fugitive loss (k_r). This is described in the following ordinary differential equation:

$$\begin{aligned} dA/dt &= -k_a A - k_r A \\ &= -(k_a + k_r) A \end{aligned} \quad \textbf{(10)}$$

Thus, as shown in Addendum 1, this differential equation leads to the following modification of Equation 9:

$$X_t = \frac{k_a A_0}{k_e - (k_a + k_r)} (e^{-(k_a + k_r) t} - e^{-k_e t}) \quad \textbf{(11)}$$

Feldmann and Maibach (1969, 1970, 1974) did not conduct i.v. elimination studies in humans for all of the compounds. For some of the compounds i.v. studies were conducted in rats and for other compounds judgement was used to estimate k_e. In the current analysis, only the 29 chemicals that included i.v. elimination studies in humans are included in the analysis.

For each of these 29 chemicals, a spreadsheet was set up in Excel and the Excel SOLVER function was used to estimate the zero-order k_a using Equations 7 as well as first-order k_a and k_r using equation 11. Because the results reported in the Feldmann and Maibach publications are expressed as the proportion of applied dose eliminated over a given period, both sides of

the Equations 7 and 11 were multiplied by k_e. In all cases, the k_e values were derived from the half-times ($t_{½}$) reported in the Feldmann and Maibach publications - i.e., $k_e = \ln(2) \div t_{½}$ - and these k_e values were used as constants rather than as parameters estimated from the models (Equations 7 and 11). The only constraint applied to the models was that k_a and k_r both must be greater than or equal to zero.

For each collection interval reported in the Feldmann and Maibach studies, time, *t*, was taken as the arithmetic average of the start and end times of the collection interval and the sum of the square of the difference between the model estimates and observed rates was minimized. Both the quasi-Newton and gradient search methods were used and other estimation factors (e.g., starting estimates of k_a and k_r, error tolerance, precision, the use of tangent versus quadratic extrapolation, and the use of forward versus central derivatives) were varied to avoid false minima.

RESULTS

The results of this analysis are summarized in Table 1. As indicated in Table 1, the data on the $K_{o/w}$ and molecular weight are taken from Durkin et al. (1995). The only change is the log $K_{o/w}$ for 2,4-D. In Durkin et al. (1995), this value is given as 2.81, which is the log $K_{o/w}$ for 2,4-D at a pH of 1. The value given in Table 1, -0.75, is the log $K_{o/w}$ for 2,4-D at a pH of 7. A pH of 7 is more appropriate for a dry deposition scenario because the pH of water on the surface of the skin, into which the 2,4-D would dissolve, will be closer to a neutral physiological pH (Emrich and Oelert 1966; Nikolajek and Emrich 1976).

In most cases (e.g., ethion, parathion, nitrobenzene) both the zero- and first-order absorption models fit the data well. For some data sets (e.g., aldrin and hexachlorophene) neither model fit the data well. In several additional cases (e.g., salicylic acid, testosterone, and progesterone) the first-order absorption model fit the data much better, compared with the zero-order absorption model. Overall, however, as summarized in Table 1, the two different models gave very similar estimates of the absorption rate coefficient, k_a. A log-log correlation of the k_a values given in Table 1 for zero-order and first-order absorption have a squared correlation coefficient of 0.97.

These similarities between the k_a values based on zero-order and first-order absorption are reflected in similar equations for estimating k_a. Unlike the earlier results of Durkin et al.(1995), both the zero-order and first-order absorption coefficients were best estimated based on both molecular weight and log $K_{o/w}$. For the zero-order absorption model, the regression was:

$$\log_{10} k_{a_{(ZeroOrder)}} = 0.203 \log_{10} K_{o/w} - 0.00559 MW - 1. \quad \textbf{(12)}$$

For the first-order absorption model with first-order fugitive loss, the regression was:

$$\log_{10} k_{a_{(FirstOrder)}} = 0.233 \log_{10} K_{o/w} - 0.00566 MW - 1. \quad \textbf{(13)}$$

For both equations, all coefficients were significant at $p < 0.004$ but the squared correlation coefficients for both models were low, about 0.32. This correlation coefficient is not remarkably lower than the squared correlation coefficient of 0.43 that is obtained for the regression of log K_p on molecular weight and log $K_{o/w}$ using Table 5-7 from U.S. EPA (1992) without censoring.

For the model based on first-order absorption with first-order fugitive loss (Equation 11), the fugitive loss rates (k_r) were not significantly correlated with either the molecular weight or the $K_{o/w}$. The observed fugitive loss rates fit a log normal distribution [$p = 0.35$ using the Kolmogorov-Smirnov test (Manugistics, Inc. 1997)] with a mean of 0.032 hour^{-1} and a 95% confidence interval 0.0028 to 0.037 hour^{-1}.

A COMPARISON OF ZERO- AND FIRST-ORDER MODELS

As in the Durkin et al. (1995) analysis, the Harris and Solomon (1992) study can be used to examine the estimates of dermal absorption based on Fick's first law and estimates based on first-order or zero-order dermal absorption rates.

Harris and Solomon (1992) had a group of five volunteers enter an area 1 hour after it was sprayed with a 190 g/L solution of 2,4-D amine at an application rate of 11 µg/cm^2. The average amount of 2,4-D as a dislodgable residue was determined by rubbing a running shoe, covered with two layers of cheesecloth, over an area 1 m^2 of the treated surface for 1 minute. Using this method, the estimated dislodgable residue was 0.85 µg/cm^2, about 7% [0.85 µg/cm^2 ÷ 11 µg/cm^2 = 0.0772] of the nominal application rate.

In the Harris and Solomon (1992) study, the five volunteers, wearing only a t-shirt and shorts and five others wearing a t-shirt, long pants, and closed footwear, were instructed to walk about on the treated surface for a period of 5 minutes then to sit or lie on the area for 5 minutes and to continue this protocol for 50 minutes more. Absorption was measured by 4-day urine collections. One of the volunteers wearing shorts and no footwear, removed his shirt 30 minutes into the exposure period but otherwise followed the protocol.

None of the volunteers wearing long pants had detectable levels of 2,4-D in their urine. Two of the five volunteers wearing only shorts and a shirt also had no detectable levels of 2,4-D in the urine. In the remaining three volunteers, the two who retained their shirts had an average absorbed dose of 1.9 μg/kg and the individual who removed his shirt absorbed a dose of 5.4 μg/kg. In the same study, volunteers were similarly subjected to the same exposure protocol 4 days after application of the 2,4-D. No 2,4-D was detected in urine samples collected over a 4-day period following exposure in any of the volunteers.

Based on the reported dislodgable residue, the transfer rate can be estimated from Equation 4 of Durkin et al. (1995) as 0.92 µg/cm^2·hour [$1.08 \cdot \log_{10}(0.85\ \mu g/cm^2) + 0.04 = -0.036$, $10^{-0.036} = 0.92$].

For the individuals wearing only shorts and a short-sleeved shirt, the estimated exposed surface area is 5300 cm^2 (U.S. EPA, 1992). For the individual who removed his shirt after 30 minutes, the average surface area of the trunk (5690 cm^2) (U.S. EPA, 1992) is added to 5300 cm^2 to yield a total exposed surface area of 10,990 cm^2 during the period over which the shirt was not worn. For the 1-hour exposure period, the average exposed surface area is taken as 8145 cm^2, the average of 5300 cm^2 (with shirt) and 10,990 cm^2 (without shirt).

Using the above transfer rate, the individuals wearing shorts and a short-sleeved shirt had an estimated exposure of 4876 µg (0.92 µg/cm^2·hour · 5300 cm^2 · 1 hour). For the individual who removed his shirt, the estimated exposure is 7501 µg (0.92 µg/cm^2·hour · 8154 cm^2 · 1 hour). Based on the analysis of the absorption kinetics of 2,4-D amine from Feldmann and Maibach (1974), the first-order absorption rate coefficient for 2,4-D is 0.00079 hour^{-1} (Table 1).

Although the duration of exposure to the contaminated vegetation was 1 hour, the true period of absorption is probably greater because it is not likely that the individuals washed completely or effectively immediately after the experiment. According to Harris and Solomon (1992), the individuals were served lunch immediately after the experiment. In addition, it is unlikely that washing would remove all of the 2,4-D. As noted by Moody et al. (1992), washing the skin with soap and water removed only about 35% of an applied dose of 2,4-D (Moody et al. 1992). On the other hand, washing may also result in an at least transient increase in the permeability of the skin to most compounds because of increased hydration of the skin (U.S. EPA 1992).

In the analysis by Durkin et al. (1995), the functional duration of exposure is taken as 4 days, the duration over which urine samples were collected. Given the uncertainties over the extent to which and the direction in which washing may have contributed to an increase or decrease in dermal absorption, this functional duration of exposure will be maintained in the current analysis.

The proportion of the deposited dose that is absorbed by time, *t*, may be calculated from Equation 8 as 0.073 [$1-e^{-0.00079*4*24}$]. Thus, for the individuals wearing shorts and a short-sleeved shirt, the absorbed dose is estimated as 5.1 µg/kg (4876 µg · 0.073 ÷ 70 kg), which is about 2.7 times greater than the observed average value of 1.9 µg/kg. For the individual who removed his shirt, the estimated absorbed dose is 7.8 µg/kg (7501 µg · 0.073 ÷ 70 kg) which is about 1.4 times greater than the observed value of 5.4 µg/kg.

Fick's first law may also be used to estimate the exposure level. Following the approach taken in Durkin et al. (1995) using the application concentration of 190 g/L (190 mg/mL or 190

mg/cm^3) and assuming an actual exposed surface area of approximately 3000 cm^2 (about 50% of the available surface area for the individuals wearing shorts and a shirt rounded to one significant place), taking the K_p of 0.00001 for 2,4-D (see Table 2), the estimated absorbed dose would be 5.7 mg (190 mg/cm^3 · 0.00001 cm/h · 1 h · 3000 cm^2) or about 0.08 mg/kg (5.7 mg ÷ 70 kg). Because, however, it is estimated that only 4876 µg or about 4.9 mg of 2,4-D was transferred to the surface of the skin, this is the maximum amount that could have been absorbed. [For this reason, the use of 190 mg/mL as the functional concentration rather than the solubility of 2,4-D in water is inconsequential.] Thus, Fick's first law estimates that all of 2,4-D transferred to the surface of the skin would be absorbed during the 1-hour exposure period: 4876 µg/70 kg or about 70 µg/kg, which overestimates the observed dose by a factor of about 37 [70 µg/kg ÷ 1.9 µg/kg].

For the individual who removed his shirt, the corresponding calculation of absorbed dose using Fick's first law would be 15.2 mg (190 mg/cm^3 · 0.00001 cm/h · 1 h · 8000 cm^2) or 15,200 µg. Again, this over-estimates the amount transferred to the skin, 7501 µg. Taking this lower value, the estimated absorbed dose would be 107 µg/kg [7501 µg ÷ 70 kg], which over-estimates the observed value of 5.4 µg/kg by a factor of about 20.

Although both methods (i.e., first-order absorption and Fick's law) are conservative as applied to this scenario and the differences between the methods are less remarkable than those in the Durkin et al. (1995) analysis, the method based on first-order dermal absorption rates yields an estimate that appears to be much more plausible and over an order of magnitude less than those based on Fick's first law.

To further compare the differences between dermal exposure estimates based on Fick's first law and those based on the assumption of first-order dermal absorption, two related exposure scenarios included in Forest Service risk assessments may be considered: wearing contaminated gloves for one hour and spilling a solution of a pesticide on to the hands then removing the unabsorbed pesticide after one hour. In both scenarios, the surface area of the hands is taken as 840 cm^2 and the body weight as 70 kg. The spill scenario assumes a retention of 0.008 mg/cm^2 from Mason and Johnson (1987). Thus, both scenarios involve exposure of the same amount of skin for the same period of time. The difference between the two scenarios is that with contaminated gloves the hands are considered to be effectively immersed. This is to say the gloves are saturated and the amount of pesticide available for absorption is essentially constant because, as the pesticide is absorbed from solution, additional contamination is assumed to occur. Hence, Fick's first law is clearly applicable. In the spill scenario, however, only a finite amount pesticide is retained on the surface of the skin and available for absorption. For such scenarios, the first-order dermal absorption model is used. Of the two scenarios, contaminated gloves would seem to present a more intense exposure than the spill scenario.

Given these exposure assumptions and using a concentration of a pesticide in solution of 0.5 mg/mL, a representative value for field solutions of many herbicides, a simulation was

conducted in which the absorbed doses were estimated from equations 2 for Fick's first law and equation 9 for first-order absorption. In the simulation, K_p's were estimated from equation 3 and k_a's were estimated from equation 13 for molecular weights ranging from 60 to 400 and log $K_{o/w}$'s ranging from -2 to 5. In the simulations, uniform distributions were used for both ranges and no correlation between molecular weight and $K_{o/w}$ was considered. This seems reasonable because for the joint data sets from the Feldmann and Maibach studies as well as the compounds used by U.S. EPA (1992), the correlation between molecular weight and $\log_{10} K_{o/w}$ is low ($r^2 \sim 0.11$). In each simulations, 1000 samples were taken.

A very high and direct correlation was found between the $\log_{10} K_{o/w}$ and the ratio of absorbed dose based on Fick's first law to the corresponding value based on first-order absorption - i.e., slope = 0.47, $r^2 = 0.998$, p-value < 0.00001. There was essentially no relationship between the molecular weight and the ratio of absorbed dose based on Fick's first law to the corresponding value based on first-order absorption - i.e., slope = -0.0004, $r^2 = 0.14$, p-value < 0.23. Over the full range of values used in the simulation, the exposures estimated using Fick's first law averages a factor of about 400 higher than those based on first-order absorption. Over a narrower range of $\log_{10} K_{o/w}$s, -2 to 0, the corresponding value was very small, a factor of only about 2.

ACIDS, ALCOHOLS, AND THEIR ESTERS

Some commercially or medicinally significant compounds are esters of weak acids or alcohols. For example, in several commercially important herbicides such as 2,4-D or triclopyr, the active ingredient is a weak organic acid. Such compounds are available in two different types of formulations: aqueous solutions of the salt of the weak acid and non-aqueous emulsifiable concentrates of the ester of the weak acid. Similarly, the hydroxyl moiety of some steroids such as hydrocortisone may be esterified with a weak acid in medicinal formulations. Relatively little information is available on the dermal absorption rate of the esters of weak acids or alcohols relative to the parent acids or alcohols.

One highly relevant study (Moody et al. 1990), however, was conducted on the dermal absorption of 2,4-D acid relative to salts and esters of 2,4-D. Using humans and experimental animals, Moody et al (1990) assayed the dermal absorption of several forms of 2,4-D in different vehicles. For each of the 2,4-D compounds tested, Moody et al (1990) report the percent recovery of the compound in the urine, the half-time, as well as the dermal absorption based on the proportion of the applied dose recovered in the urine after 14 days and the assumption of first-order absorption. The study by Moody et al (1990) was conducted following a protocol similar to that of Feldmann and Maibach (1974), except that a 14-day post-exposure collection period was used rather than a 5-day period as in the Feldmann and Maibach studies. Unlike the Feldmann and Maibach (1974) paper, the publication by Moody et al. (1990) does not provide data regarding the amounts of compound eliminated after various time periods.

In the Moody et al. (1990) study, there are very substantial inconsistencies among the acid or amine versus the ester formulation. Very little difference in dermal absorption was noted when the acid, amine salt, and isooctyl ester were applied to the backs of rabbits. Nonetheless, when applied to the human forehead, the 2,4-D amine was absorbed to a much greater extent than the isooctyl ester, either in acetone or an Esteron LV96 (commerical carrier) blank. In monkeys, the absorption of the amine and isooctyl forms were comparable when applied to the forehead but the isooctyl form was much more readily absorbed than the amine salt when applied to the forearm. The difference between the absorption rate of 2,4-D acid and the isooctyl ester after application to the monkey forearm, however, was modest. The highest cumulative absorption reported by Moody et al. (1990) is about 58% (2,4-D amine in water on the forehead of humans), which is almost the same as the 56% absorption of 2,4-D isooctyl ester in acetone applied to the forehead of monkeys (Moody et al. 1990).

Although there is no information regarding the absorption of other esters of weak acids, Feldmann and Maibach (1969) did assay the absorption of hydrocortisone and testosterone as well as the esters of these compounds. The investigators report that the dermal absorption of hydrocortisone was substantially less than the dermal absorption of hydrocortisone acetate. Testosterone, however, was absorbed to a substantially greater extent than either of its esters. Thus, while the lipophilicity of the esters is greater than that of the parent compound for both testosterone and hydrocortisone and the esters of both of these compounds are estimated to have a greater K_p than the corresponding parent compound (i.e., Equation 2), the relative dermal absorption rates of these compounds and their esters is inconsistent.

Because the reported differences in absorption rates among species, sites, and forms of 2,4-D are not consistent (Moody et al. 1990, 1992) and because of the inconsistent relationship noted by Feldmann and Maibach (1969) in the dermal absorption of hydrocortisone and testosterone, compared with esters of these compounds, the predictive value of Equation 13 for esters of herbicides or other compounds is questionable. For example, based on Equation 14, 2,4-D acid (MW = 221, log K_{ow} at pH 7 = -0.75) is estimated to have a first-order absorption rate coefficient of 0.0012 $hour^{-1}$. The isooctyl ester of 2,4-D (MW = 333, log K_{ow} = 6.73), on the other hand, is estimated to have a first-order absorption rate coefficient of 0.0156 $hour^{-1}$, which is 10 times greater than that of the acid. Based on the study by Moody et al. (1990), the difference does not seem credible.

DISCUSSION and CONCLUSION

The reanalysis of the Feldmann and Maibach data summarized here is based on estimated absorption rate coefficients rather than simple observed absorption rates, as well as a much less arbitrary censoring of the data. In addition, the equations that describe the relationship of the absorption rate coefficients to physicochemical properties (Equations 12 and 13) are qualitatively similar to the equations recommended by U.S. EPA (1992) in the estimation of dermal permeability. This finding is intuitively reasonable because the factors that influence dermal permeability should correspond to the factors that influence dermal absorption.

As discussed by U.S. EPA (1992), the underlying processes involved in dermal absorption are likely to be zero-order in cases where the individual is effectively immersed in a large volume of contaminated fluid. In other words, if solution of a chemical effectively covers the surface of the skin at a constant concentration, a constant amount is likely to be absorbed per unit time. The amount that is absorbed will depend on the physicochemical properties rather the amount of chemical on the skin, so long as the surface of the skin is coated. This is the basic premise behind the use of Fick's first law.

While the Feldmann and Maibach data can be analyzed using a zero-order absorption model (i.e. Equation 12), this analysis must be based on the proportion of the applied dose rather than the absolute amount absorbed per unit time and unit of skin surface. This limitation is imposed by the level of detail presented in the Feldmann and Maibach publications.

The first-order absorption model modified to consider a fugitive loss rate (Equation 11) fits the Feldmann and Maibach data reasonably well and can be applied to estimate general absorption rate coefficients with the data presented in the Feldmann and Maibach publications. Based on a reassessment of the Harris and Solomon (1992) study, the approach based on first-order absorption may yield more realistic exposure assessments in cases where the skin is not effectively saturated. This application of first-order absorption kinetics assumes a very different biological process from that assumed by zero-order absorption. Rather than viewing the skin as a simple membrane coated with a substance, the application of first-order absorption kinetics implicitly assumes that some amount of a compound is deposited on the surface of the skin then relatively rapidly incorporated into the layers of the skin or some subset of these layers. In other words, the compound is effectively distributed in the skin at some initial concentration. In this biological construct, the rate at which the compound is redistributed to the systemic circulation at time *t* will be dependent on the concentration in the skin at time *t* and thus first- rather than zero-order kinetics will be applicable.

In some cases, there will be relatively little difference between exposure assessments for comparable exposure scenarios based on Fick's first law and those based on the assumption of first-order dermal absorption. The basic interpretation from the simulations described above is that dermal absorption estimates based on Fick's first law and the assumption of first-order dermal absorption will be similar for relatively lipophobic ($\log_{10}$ Ko/w between -2 and 0) compounds. This seems sensible over short periods of exposure because such compounds will be absorbed at a very slow rate, regardless of how the rate is expressed kineticly. Under the assumption of first-order absorption, a poorly absorbed compound is likely to present in the skin surface at a concentration or amount that decreases very slowly. This, at least for short periods of exposure relative to the rate of absorption, will effectively reduce to a constant or zero-order absorption rate.

The data set from Feldmann and Maibach (1969, 1970, and 1974) that serves as the basis for estimating k_a is the most extensive and relevant series of studies that has ever been conducted on *in vivo* dermal absorption in humans. Particularly for dry deposition scenarios, it seems

reasonable to attempt to use the reported data as fully as possible in human health risk assessments. While the correlation coefficient for estimating the first-order absorption rate coefficient, k_a, is admittedly low (≈ 0.32), Equation 13 is nonetheless statistically significant ($p = 0.0028$) and can be used with greater confidence than Equation 4 from Durkin et al. (1995). The uncertainties in the estimate of k_a or analogous estimates of K_p from Equation 3 should, of course, be considered quantitatively in the risk assessment whenever this equation is used (Addendum 2).

When estimates of k_a are obtained from Equation 13 and used to estimate absorbed dose with Equation 8, the estimates are likely to be conservative because Equation 13 is based on estimates of k_a that incorporate fugitive losses (k_r) from the surface of the skin (Equation 11) and Equation 8 does not consider such losses. As indicated in Table 1, the values for k_r derived from the Feldmann and Maibach studies are typically greater than the dermal absorption rates (k_a) by an order of magnitude or more. The rates of fugitive loss, however, are likely to be highly variable, depending on the activities of the individuals after exposure. If fugitive loss rate coefficients are used in an exposure assessment, the justification for selecting a specific rate will be specific to assumptions used in the risk assessment. In other words, a basis for recommending 'generic' values for k_r is not apparent.

As with any simple empirical approach to estimating a complex biological process such as dermal absorption, the estimate should be regarded with substantial skepticism. The need to use algorithms such as Equations 3 or 13 suggest a lack of knowledge and substantial uncertainty. While statistical variability can be reflected relatively simply (Addendum 2), this does not encompass all of the uncertainty. For example, as discussed above, Equations 3 and 13 may yield unreliable estimates of dermal absorption *in vivo* that would not be reflected in statistical confidence intervals. While somewhat speculative, this may reflect chemical or biological processes that either alter the applied compound - e.g., hydrolysis of an ester - or influence the kinetics of the compound in ways that the empirical algorithm may not reflect - e.g., protein binding. In any event, while the equations developed in this paper or similar equations developed by others may be used to estimate parameters in the absence of data, they may be poor substitutes for experimental data and their use substantially adds to the uncertainties in the risk assessment process.

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Table 1: Chemicals used in the analysis of dermal absorption rates (based on data summarized in Durkin et al. 1995 and the dermal absorption studies conducted by Feldmann and Maibach 1969, 1970, and 1974).

Chemical	MW	log $K_{o/w}$	Zero-Order[1]	First-Order[2]	
			k_a ($hour^{-1}$)	k_a ($hour^{-1}$)	k_r ($hour^{-1}$)
Azodrin	223.17	-1.31	0.002666	0.003515	0.016
Ethion	384.46	5.07	0.000550	0.000732	0.018
Guthion	317.32	2.75	0.014471	0.022977	0.11
Malathion	330.35	2.36	0.004604	0.006409	0.079
Parathion	291.26	3.83	0.003596	0.004065	0.039
Baygon	209.25	1.45	0.019435	0.032761	0.11
Carbaryl	201.23	2.36	0.046549	0.058040	0.015
Aldrin	364.92	6.50	0.000790	0.001167	0.0092
Dieldrin	380.91	5.40	0.029604	0.079391	1.1
Lindane	290.83	3.72	0.009483	0.072700	1.0
2,4-D	221.04	-0.75	0.000731	0.000790	0.0066
Diquat	344.05	-2.82	0.000041	0.000054	0.015
Caffeine	194.19	-0.07	0.014676	0.019865	0.017
Chloramphenicol	323.13	1.14	0.000195	0.000231	0.0047
Colchicine	399.45	1.03	0.000364	0.000526	0.011
N,N-diethyl toluamide	191.28	2.26	0.011958	0.019174	0.13
Dinitrochlorobenzene	202.55	2.27	0.053369	0.171538	0.22
Hexachlorophene	406.91	6.91	0.000605	0.001316	0.025
Nitrobenzene	123.11	1.85	0.001172	0.001537	0.13
Potassium thiocyanate	97.18	-0.82	0.000987	0.001027	0.0
Salicylic acid	138.12	2.26	0.004046	0.005146	0.013
Urea	60.06	-2.11	0.000586	0.000547	0.0
Hydrocortisone	362.47	1.61	0.000169	0.000221	0.0052
Hydrocortisone acetate	404.51	2.30	0.000801	0.000872	0.023
Estradiol	272.39	3.94	0.000965	0.001008	0.0
Testosterone	288.43	3.32	0.003327	0.003971	0.024
Fluocinoloneacetonide	452.50	2.56	0.000115	0.000131	0.0047
Dexamethasone	391.46	1.83	0.000035	0.000055	0.012
Progesterone	314.45	3.77	0.002241	0.003976	0.032

[1] Calculated using Equation 7. Reported as proportion of applied dose per hour rather than amount per hour.

[2] First-order absorption rate coefficient (k_a) and first-order fugitive loss rate (k_r) using Equation 13.

Addendum 1: Fugitive Loss with First-Order Absorption and First-Order Elimination

The rate of change in the amount of chemical on the surface of the skin at time *t* (*dA/dt*) is determined by the amount remaining on the skin at time t (*A*), the absorption rate coefficient (k_a), and the first-order fugitive loss rate coefficient (k_r):

$$\begin{aligned} dA/dt &= -k_a A - k_r A \\ &= -(k_a + k_r)A \end{aligned} \qquad \textbf{(1)}$$

The integral of this first-order differential equation is:

$$A = A_0 e^{-(k_a + k_e)t} \qquad \textbf{(2)}$$

Substituting the right side of equation 1 into the left side of equation 2,

$$\begin{aligned} \frac{dX}{dt} &= k_a A_0 e^{-(k_a + k_r)t} - k_e X \\ &\quad or \\ \frac{dX}{dt} + k_e X &= k_a A_0 e^{-(k_a + k_r)t} \end{aligned} \qquad \textbf{(3)}$$

Since the term ($k_a + k_r$) can be regarded as a constant, *k*, at least for the purposes of integration, the integrating factor is $e^{dPdt} = e^{dkdt} = e^{k_e t}$. Multiplying both sides of equation 3 by the integrating factor,

$$\begin{aligned} \frac{d(e^{k_e t}X)}{dt} &= e^{k_e t}\left[\frac{dX}{dt} + k_e X\right] \\ &= e^{k_e t} \cdot k_a A_0 e^{-(k_a + k_r)t} \end{aligned} \qquad \textbf{(4)}$$

The integral of this equation is ,

$$\begin{aligned} Xe^{k_e t} &= k_a A_0 \int e^{(k_e - (k_a + k_r))t} \cdot dt \\ &= \left(\frac{k_a A_0}{k_e - (k_a + k_r)}\right)(e^{(k_e - (k_a + k_r))t}) + c \end{aligned} \qquad \textbf{(5)}$$

and the constant of integration ($t = 0$) is thus

$$\frac{-k_a A_0}{k_e - (k_a + k_r)} = c. \qquad \textbf{(6)}$$

Substituting equation 6 into equation 5,

$$Xe^{k_e t} = \left(\frac{k_a A_0}{k_e - (k_a + k_r)} \right) (e^{(k_e - (k_a + k_r))t}) - \frac{k_a A_0}{k_e - (k_a + k_r)} \quad \textbf{(7)}$$

$$Xe^{k_e t} = \frac{(k_a A_0)(e^{(k_e - (k_a + k_r))t}) - k_a A_0}{k_e - (k_a + k_r)} \quad \textbf{(8)}$$

$$Xe^{k_e t} = \frac{(k_a A_0)(e^{(k_e - (k_a + k_r)t} - 1)}{k_e - (k_a + k_r)} \quad \textbf{(9)}$$

$$Xe^{k_e t} = \frac{k_a A_0}{k_e - (k_a + k_r)} (e^{(k_e - (k_a + k_r))t} - 1) \quad \textbf{(10)}$$

$$X = \frac{k_a A_0}{k_e - (k_a + k_r)} \cdot \frac{(e^{(k_e - (k_a + k_r))t} - 1)}{e^{k_e t}} \quad \textbf{(11)}$$

$$X = \frac{k_a A_0}{k_e - (k_a + k_r)} (e^{-(k_a + k_r)t} - e^{-k_e t}) \quad \textbf{(12)}$$

Addendum 2: Confidence intervals for k_a or K_p.

The confidence intervals for k_a from equation 13 in the main body of the paper may be calculated as with any multiple linear regression (e.g., Mendenhall and Scheaffer 1973) using least squares:

$$\hat{y} \pm t_{\alpha/2} s \sqrt{a'(X'X)^{-1}a}$$

where $t_{\alpha/2}$ is the critical value of the t-distribution, s is the standard deviation of the model - i.e., the square route of the standard error of the estimate (SSE) divided by the degrees of freedom of the model - **a** is a column vector of constants for which the confidence interval is being estimated, and **X** is an array of independent variables the first column of which are all ones (1's) if a constant is included in the model, as is the case with equation 13. When applied to equation 13, the second and third columns are the molecular weights and $\log_{10} K_{o/w}$'s respectively. This ordering is required because of the data matrix, **X**, used to generate $\mathbf{X'X}^{-1}$ contained the molecular weight in the second column and the $\log_{10} K_{o/w}$ in the third column - i.e., as in Table 1. The expressions **a'** and **X'** refer to the transposes of **a** and **X** respectively.

Since the model is based on 29 observations and estimates three parameters, there are 26 degrees of freedom. The standard error of the estimate is 16.1125 and thus the mean square error or model variance is 0.61971 [16.1125/26] and the standard deviation (s) is 0.7872 [$0.61971^{0.5}$]. For data used to generate equation 13 - i.e., Table 1 of the paper - $(X'X)^{-1}$ is equal to:

$$\begin{matrix} 0.31 & -0.0010 & 0.0082 \\ -0.0010 & 0.0000043 & -0.000094 \\ 0.0082 & -0.000094 & 0.0085 \end{matrix}$$

The value of **a** will depend on the point for which the confidence intervals are to be calculated.

The term $\mathbf{a'}\cdot(\mathbf{X'X})^{-1}\cdot\mathbf{a}$ requires matrix multiplication. While this is most easily accomplished using a program that does matrix arithmetic, the calculation can be done with a standard calculator. Letting

$$\mathbf{a} = \{a1, a2, a3\}$$

and

$$(\mathbf{X'X})^{-1} = \{ \{b1, b2, b3\}, \{c1, c2, c3\}, \{d1, d2, d3\} \},$$

$\mathbf{a'}\cdot(\mathbf{X'X})^{-1}\cdot\mathbf{a}$ is equal to

$$a1\,(a1b1 + a2c1 + a3d1) +$$

$$a2\,(a1b2 + a2c2 + a3d2) + a3\,(a1b3 + a2c3 + a3d3).$$

The above solution was obtained using the symbolic matrix manipulation capabilities of Mathematica, Version 3 (Wolfram 1996).

For example, the 95% confidence limits ($\alpha = 0.05$) on k_a may be calculated for 2,4-D. The maximum likelihood estimate of the k_a for 2,4-D is 0.0012 $hour^{-1}$, the $\log_{10}$ of which is -2.92. For 2,4-D, **a** is equal to {1, 221, -0.75}, where 221 is the molecular weight and -0.75 is the log of the $K_{o/w}$. The critical value for $t_{0.025}$ at 26 degrees of freedom is used, 2.056, and the model standard deviation, as indicated above, is 0.7872. Using the above equation for calculating the confidence intervals and making the appropriate matrix multiplications, the term on the right hand side of the ± symbol is approximately 0.484. Thus, the 95% confidence interval for k_a is 0.00039 to 0.0037, spanning a factor of about 9.2.

A similar approach may be taken to obtaining confidence intervals for K_p (Equation 3). A noted in the main body of this paper, this equation is derived from 90 data points - i.e., 87 degrees of freedom using the data in Table 5-4 in U.S. EPA 1992 but omitting the three outliers. An analyses of these data in Mathematica, Version 3 (Wolfram 1996) as well as STATGRAPHICS (Manugistics, Inc. 1997) yields a standard error of the estimate of 45.9983. Thus, the mean square error or model variance is 0.528716 [45.9983/87] and the standard deviation (s) is 0.727129 [$0.528716^{0.5}$]. For data used to generate equation 3 $(X'X)^{-1}$ is equal to:

$$\begin{bmatrix} 0.0550931 & -0.000094155 & -0.0103443 \\ -0.000094155 & 0.0000005978 & -0.00002225 \\ -0.0103443 & -0.00002225 & 0.00740677 \end{bmatrix}$$

As with the above example for the k_a, the values in the vector **a** must be 1, followed by the molecular weight, which is in turn followed by the $\log_{10} K_{o/w}$.