2026

Evaluation of Method Efficiency Adjustment and Application to Exposure Data

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

March 24, 2026

MEMORANDUM

SUBJECT: Evaluation of Method Efficiency Adjustment (MEA) And Application to Exposure Data in Response to Task Force/Stakeholder Submissions (MRIDs 49173001, 52028103, 52028102, & 52321101).

PC Code: NA
Decision No.: NA
Petition No.: NA
Risk Assessment Type: NA
MRID No.: 49173001, 52028103, 52028102, 52321101

Task Group No.: TG00661153
Parent Case No.: TG00661001
DP Barcode.: D466625
TXR No.: NA
40 CFR: NA

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The conclusions conveyed in this assessment were developed in full compliance with EPA's Scientific Integrity Policy for Transparent and Objective Science, and the EPA's Scientific Integrity Program's Approaches for Expressing and Resolving Differing Scientific Opinions. The full text of EPA's Scientific Integrity Policy for Transparent and Objective Science, as updated and approved by the Scientific Integrity Committee and EPA's Science Advisor can be found here: https://www.epa.gov/scientific-integrity/epas-scientific-integrity-policy. The full text of the EPA's Scientific Integrity Program's Approaches for Expressing and Resolving Differing Scientific Opinions can be found here: https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions.

Note: This memorandum was reviewed by the Exposure Science Advisory Committee (ExpoSAC) on October 3, 2024.

Table of Contents

1.0 Executive Summary

Dermal and inhalation exposure monitoring data used for U.S. EPA regulatory pesticide risk assessments have been developed over several decades via collaborative efforts with multiple regulatory agencies and industry task forces. These efforts have resulted in one of the largest compilations of exposure data available globally and are reflected in the current methods EPA uses to conduct pesticide exposure assessment.[1] During the development and conduct of these monitoring studies, questions were raised regarding the ability of certain dermal exposure monitoring methods (e.g., hand rinse and face/neck wipe methods that sample bare skin) to accurately represent the expected exposure due to the potential for dermal absorption prior to the sampling. These issues were primarily raised during the Agency's peer review of exposure monitoring protocols submitted to the Human Studies Review Board (HSRB)[2] in 2006 by the Agricultural Handlers Exposure Task Force (AHETF).[3] EPA addressed these uncertainties via application of the *Method Efficiency Adjustment (MEA)*, an upward-adjustment, or correction, to the dermal exposure monitoring results. Specifically, when applied to exposure monitoring data, the MEA attempts to correct for the potential underestimation of exposure due to dermal absorption-related limitations associated with the commonly used face/neck wipe and hand rinse techniques intended to remove pesticide exposure from bare skin. Over half of the scenarios are impacted in some manner by the application of the MEA, resulting in a higher dermal exposure metric than actually measured.

Since EPA began applying the MEA to dermal exposure monitoring results (ca. 2007), EPA has received various comments and submissions from pesticide industry stakeholders stating that the MEA is unnecessary and that the dermal exposure monitoring methods in question are sufficiently reliable without any adjustments. Formal comments have come from the AHETF (as their studies have been primarily affected thus far), first in 2013 (Canez, 2013; EPA MRID 49173001), followed by letters to EPA in 2014 and 2015 (EPA MRID 52028103), as well as a follow-up submission in 2022 (EPA MRID 52028102), and another letter to EPA in 2024 (EPA MRID 52321101).[4] This paper serves as a review and response to those submissions.

EPA continues to believe that exposure monitoring techniques that directly sample the skin (e.g., face/neck wipes and hand rinses) have dermal absorption-related limitations as discussed in this review. However, the current application of MEA (i.e., as a 2X increase to exposure measurements based on an assumption the sampling may underestimate exposure collection by 50%) overstates these limitations. Based on a number of considerations outlined in this document, EPA will revise the MEA to a dermal loading-based approach. A generic dermal absorption model has been developed that will allow for individual-specific adjustments, based on dermal skin loading and exposure time for the monitored individual. Ultimately, EPA will adjust each worker's measured hand and head exposure (expressed as a dermal loading estimate in µg/cm^2) with a potential absorption estimate from the modeling discussed in this analysis. Instead of the one-size-fits-all 2X MEA currently applied, the generic dermal absorption model discussed in this analysis will be used to determine the appropriate

[1] The following site describes how task force results are used in exposure assessment process: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data.

[2] Meeting Materials: https://archive.epa.gov/osa/hsrb/web/html/jun-27-30-2006-public-meeting.html Meeting Minutes: https://archive.epa.gov/osa/hsrb/web/pdf/finaljuneminutes72506-2.pdf.

[3] Note that there will be a discussion of the data generated by other task forces in this document which will be explained.

[4] Note that this letter was a resubmission of a letter dated January 3, 2024.

adjustment factor. For example, a hand exposure measurement estimated to be 10 µg/cm^2 would be adjusted by a factor of 1.1X (corresponding to approximately 7% dermal absorption), while a hand exposure measurement of 0.01 µg/cm^2 would be adjusted by a factor of 2.3X (corresponding to approximately 56% absorption). This represents a refinement of the existing MEA approach, while still recognizing the potential for additional case-specific refinements and for methodological validation studies that could obviate the need for MEA by directly demonstrating the efficiency and reliability of the face/neck wipe and hand rinse. Going forward, datasets currently using MEA will be revised, and MEA will now also be considered for datasets where it has yet to be applied.

2.0 Background

For regulatory use, where exposure monitoring data for some pesticides are used to estimate exposure for any pesticide, dermal exposure monitoring methods should reliably intercept dermal exposure (i.e., capture "what lands on the skin") when being used in a "generic" manner to support the registration of any pesticide. These methods contrast with biomonitoring strategies (e.g., collection of urine or blood) which can be used to quantify chemical-specific conditions such as absorption, metabolism, and excretion, but are less useful for "generic" purposes. The employment of different exposure collection methods for different body parts has developed over time, considering both analytical capabilities as well as study participant logistics. In more contemporary pesticide exposure monitoring studies, exposure to the hands is measured using a rinse method, and exposure to the face/neck is measured using a wipe method. Both removal-style methods directly sample the participants' skin and attempt to remove residues resulting from exposure. Exposure to the rest of the body (e.g., arms, legs, torso) is often measured using interception-style methods, such as cloth whole-body dosimeters (WBD). In contrast to removal-style methods, interception-style methods more directly intercept exposure that would have otherwise landed on the individual's skin. Interception-style methods for the head and hands such as cotton gloves, cloth hoods, and cloth patches have been utilized in the past, but were historically difficult in practice due to interference with participants' abilities to perform the activities being monitored. Cloth hoods had the potential to reduce visibility, cloth head patches were difficult to secure, and cotton gloves under chemical-resistant gloves reduced dexterity. Over time researchers largely settled on the removal-style hand rinse and face/neck wipe methods, which avoided many of these logistical issues. The application of MEA to correct exposure measurements is relevant to these removal-style methods, not interception-style methods.

Uncertainties regarding the hand rinse and face/neck wipe sampling methodologies were raised in a 2006 meeting with the EPA HSRB on proposed occupational pesticide exposure studies by the AHETF.[5] While measurement of the body using WBD was less concerning, questions regarding the reliability of the hand rinse and face/neck wipe methods were raised. The following is an excerpt from the meeting minutes:

> "Hand washing also underestimates exposure. A removal efficiency study could be conducted to correct for this. Dr. Fenske believed that the 4-hour exposure duration was reasonable and allowed investigators the time they needed to set up and take measurements. Dr. Fenske also

[5] Meeting Materials: https://archive.epa.gov/osa/hsrb/web/html/jun-27-30-2006-public-meeting.html Meeting Minutes: https://archive.epa.gov/osa/hsrb/web/pdf/finaljuneminutes72506-2.pdf

> raised issues on over and underestimation of exposure, based on the study design and estimates of exposure from hand and neck wipes, and hand rinsing."

Due to the HSRB's findings on this issue and a variety of other topics raised in the 2006 HSRB report, in January 2007 EPA asked the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) to review the protocols, supporting methods, and procedures planned for use by two industry-based task forces focused on collecting exposure data. These task forces were gathering exposure data for conventional pesticides (AHETF) and antimicrobial pesticides (Antimicrobial Exposure Assessment Task Force – AEATF). The following is an excerpt of the 2007 SAP meeting minutes: [6]

> "The Panel was slightly more equivocal about a need to correct handwashing for its efficiency at recovering pesticides from the skin. Existing data clearly indicate that adsorption of certain pesticides can occur within a matter of minutes after the exposure, that hand wiping underestimates dermal exposure more than does hand washing, and that recovery efficiency is really not a constant…….Overall, the Panel recommended that use of a hand washing technique should be accepted in AHETF or AEATF studies if it is supported by either laboratory data and/or a model that predicts and can correct for its efficiency over the sampling time for the pesticide being studied."

In June of 2007, EPA returned to the HSRB for additional review of the approaches used by the task forces.[7] EPA discussed the need for the proposed task force research to assess the potential for underestimation of exposure by the hand rinse and face/neck wipe due to dermal absorption of the surrogate material during the exposure period. Because of a lack of appropriate information at that time, EPA proposed a proactive approach where hand rinse and face/neck wipe exposure results would be automatically corrected/adjusted. This correction, known as the MEA, was intended to account for the uncertainty associated with sampling inefficiency of the hand rinse and face/neck wipe (i.e., dermal sampling methods that employ physical removal of residues from skin using mechanical agitation and an aqueous surfactant); no correction was proposed for results based on dosimeter methods or other methods where removal of residues from skin was not performed. Additionally, EPA proposed the MEA only in cases when hand and head measurements contribute significantly to total dermal exposure. The HSRB accepted this approach. The proposed adjustment was as follows:

"For hand wash and face/neck wipe samples, EPA proposes the following conditions:

1. if measured exposures from hands, face, and neck contribute less than 20 percent of total dermal exposure, no action is required,
2. if measured exposure contribution represents between 20 and 60 percent of total dermal exposure[8], an automatic 50 percent adjustment will be made or the AHETF can submit a validation study, and

[6] https://www.regulations.gov/document?D=EPA-HQ-OPP-2006-0856-0079

[7] General information on meeting: https://archive.epa.gov/osa/hsrb/web/html/jun-27-29-2007-public-meeting.html
Transmittal memo: https://archive.epa.gov/osa/hsrb/web/pdf/transmittal-memo.pdf
Meeting minutes: https://archive.epa.gov/osa/hsrb/web/pdf/hsrb-june2007minutes8707final.pdf

[8] These percentages were proposed based on pragmatic considerations rather than any quantitative analysis.

3. if measured exposure contribution is greater than 60 percent, a validation study is required."[9]

As a consequence of the HSRB and SAP reviews, and the proposal outlined above, EPA has applied the MEA for recent data submissions, assuming 50% method inefficiency, thereby doubling the hand and head measurements when the contribution to total dermal exposure is 20% or more. Given existing knowledge of dermal absorption, the 50% adjustment value was considered an upper-bound selection meant to result in a health-protective adjustment factor for the potential method inefficiency. In effect, doubling these measurements implies that approximately half of the participants' exposure is "missed" by the collection method due to absorption through the skin into the body. However, pesticide industry stakeholders have contested this approach for various reasons, stating that the removal methods are adequately reliable for generic databases.

2.1 Impact of the MEA

In the context of evaluating the continuation of the MEA, it is important to consider both the impact the approach has had thus far as well as the potential future impact if adopted more widely. EPA uses pesticide exposure monitoring studies as the basis for models that predict exposure in occupational and residential settings. The AHETF has produced much of the data for assessing exposure for workers who "handle" pesticides (i.e., who mix, load, and apply pesticides). The metrics used as a basic model for pesticide handlers are known as "unit exposures," expressed as microgram pesticide exposure per pound of pesticide handled. For other occupational settings, such as hand labor in previously treated fields (e.g., vegetable harvest), different exposure metrics are used, called "transfer coefficients" (TCs), based on exposure monitoring studies conducted by the Agricultural Reentry Task Force (ARTF).[10] EPA also evaluates exposures for pesticides used in residential settings as outlined in guidance known as the *Standard Operating Procedures For Residential Pesticide Exposure Assessment (SOPs).*[11] Some of the exposure metrics in the SOPs were generated by a separate industry task force called the Outdoor Residential Exposure Task Force (ORETF). Beyond data generated by industry task forces, EPA relies upon information from many chemical-specific studies generated outside of task force efforts. Currently, EPA has applied the MEA to correct only AHETF exposure metrics as identified through the HSRB and SAP reviews. EPA has yet to consider this adjustment universally across all datasets (e.g., ARTF, ORETF, Residential SOPs) but to the extent MEA has merit and is further applied, the impact would extend to these other data. Below we characterize the current impact to AHETF exposure metrics.

The AHETF is a task force which was formed under FIFRA guidance whose membership contains the majority of pesticide industry registrants both on a domestic and global scale.[12] The purpose of the AHETF was to develop scenario-specific occupational handler exposure data intended for use generically to support the registration of *any* pesticide. The exposure conditions reflect the equipment used (e.g., ground sprayer, handheld sprayer, aircraft, etc.) and the type of clothing and/or protective

[9] To date a validation study has not been required or conducted. In practice, the automatic 50% adjustment has been employed when combined head and hand exposures are 20% or more.

[10] See the following for information on ARTF https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

[11] See the following for information on the SOPs https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[12] Exposure Task Force - Exposure Task Force (exposuretf.com)

equipment used. The resulting exposure data are used by EPA in pesticide risk assessments and are publicly available in the *Occupational Pesticide Handler Unit Exposure Surrogate Reference Table*.[13] The "Surrogate Table" lists almost 40 major scenario categories delineated based on activity, equipment, packaging, or formulation. Figure 1 below illustrates how EPA has indicated whether the MEA has been applied to the exposure monitoring studies underlying the various scenarios in the Surrogate Table.

Figure 1. Excerpt from May 2021 Surrogate Reference Table Noting Application of the MEA

Exposure Route	Personal Protective Equipment (PPE) Level[2]	Data Source[3,4,5]	Statistic	Unit Exposure (µg/lb ai)
Dermal	Single layer, no gloves (A)	AHETF (MEA)	Mean	227
	Single layer, gloves	AHETF (MEA)	Mean	51.6
	Double layer, gloves (B)	AHETF (MEA)	Mean	41.2
	Engineering control (water-soluble packaging)	AHETF (MEA)	Mean	12.5

Over half of the scenarios are impacted in some manner by the application of the MEA, resulting in a higher dermal exposure metric than actually measured. That is, over half of the data reported that hand and head exposure accounted for at least 20% of the total dermal exposure. Thus, those hand and head exposure estimates were doubled to account for the assumed collection method inefficiency. Similarly, in 2013, the AHETF submitted data from exposure monitoring studies of pesticide seed treatment, which EPA accepted for generic use and began using in January 2022. Review of these data included consideration of MEA which was ultimately applied for all of the seed treatment scenarios. Documentation is provided in the reviews of those studies.[14] As noted by the AHETF in their most recent 2022 submission, use of the MEA for the seed treatment exposure monitoring studies has a significant impact.

For many individual workers monitored in AHETF studies, including the seed treatment exposure studies, exposure contributions from the hand and head account for a very large percentage of the total dermal exposure (e.g., > 80%). In those cases especially, the 2-fold MEA increase of the hand and head exposure has a significant impact on the total dermal exposure. This can have a significant downstream impact on regulatory decisions made by EPA for those who use pesticides. The list below identifies the exposure scenarios impacted by the application of the MEA.

- Mixing/loading dry flowables
- Mixing/loading granules
- Mixing/loading liquids – open system
- Mixing/loading liquids – closed system
- Mixing/loading microencapsulants – open system
- Mixing/loading microencapsulants – closed system
- Mixing/loading water soluble packets
- Application – Aerial
- Application – Open cab airblast
- Application – Closed cab airblast
- Application – Pour on Liquid
- Application – Granule
- Application – Dust
- Application – Animal Back Rubber
- Application – Animal Dip
- Application - Animal Dust Bag
- Application – Animal Feed Through Dust, Granule, & Liquid
- Application – Animal Granules
- Commercial seed treating – All formulations
- Commercial seed packaging – All formulations

[13] https://www.epa.gov/sites/production/files/2018-06/documents/opp-hed-pesticide-handler-surrogate-unit-exposure-table-june-2018.pdf
[14] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-exposure-seed-treatment

- Application – Open cab groundboom
- Mix/load/apply – Right of Way plus other sites, Backpack
- Mix/load/apply – Mechanical Handgun (e.g., Right of Way)
- Mix/load/apply – Landscaping plus other sites, Mechanical Handgun Landscaping
- Application – Truck Fogger
- Commercial seed equipment cleaning – All formulations
- Loading and planting of commercially treated seed – All formulations
- On-Farm seed treating and planting – liquids
- On-Farm seed treating and planting - solids

Some of these scenarios are relatively minor pesticide use patterns; however, some represent predominating agricultural pesticide use scenarios where the application of the MEA can significantly impact the estimated dermal exposure which can then affect the outcome of the regulatory decision-making process.

The impact of the MEA on select examples of major agricultural use patterns has been compiled in Table 2 below. The differences in exposure values with and without the MEA applied to individual subject data clearly illustrate that application of the MEA can have a major impact on final regulatory decisions given it increases total dermal exposure estimates in the selected examples by at least 27.3% and as much as 75% (i.e., a 1.3- to 1.8-fold increase). Thus, the MEA can have a significant impact on dermal exposure for some pesticide exposure scenarios when study participants' exposure is concentrated on the hands or head (i.e., ≥20% on body parts where sampling is performed on the bare skin).

Table 2: Impact of MEA For Example Predominant Agricultural Use Patterns

Scenario	# Individuals Monitored	Average MEA Impact on Individual's Exposure Estimate (fold change)
Open Pour Granular Mixing/Loading – Single Layer Clothing, Gloves	21	30.6 % exposure increase (1.3X)
Closed Cab Airblast Application – Single Layer Clothing, No Gloves In Closed Tractor Cab	24	53.7 % exposure increase (1.5X)
Closed Cockpit Aerial Application – Single Layer Clothing, No Gloves In Closed Cockpit Plane/Helicopter	42	68.3 % exposure increase (1.7X)
Backpack Application To Rights of Way Areas - Single Layer Clothing, Gloves	19	27.3 % exposure increase (1.3X)
Commercial Seed Treatment – Treating Seed	119	46.3 % exposure increase (1.5X)
Commercial Seed Treatment – Cleaning Equipment	75	75 % exposure increase (1.8X)
On-Farm Seed Treatment (Liquids)	48	47.1 % exposure increase (1.5X)

2.2 Stakeholder Comments on MEA

EPA has been routinely applying the MEA since its proposal in 2007. As the MEA has been largely applied to their studies, the AHETF in particular has critiqued this approach both in meetings with the EPA and in formal submissions. In a 2010 meeting, the AHETF proposed judging the reliability of the monitoring study residue removal techniques based on standard guideline dermal absorption studies[15] across a wide variety of pesticide chemicals. This was based on the premise that the in-field exposure monitoring studies and the laboratory dermal absorption data utilize analogous skin residue removal

[15] Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Guideline 870.7600 Dermal Penetration. Organization for Economic Cooperation and Development (OECD) Guidelines 427 (in vivo) and 428 (in vitro).

techniques. The AHETF's conclusion was that, in general, laboratory dermal absorption studies demonstrate that pesticides are not well absorbed through the skin, and, therefore, as the wash-off methods are analogous in each, the removal methods employed in exposure monitoring studies that remove residues as a result of exposure from bare skin would adequately capture the potential dermal exposure. EPA considered this proposal and conducted a separate statistical analysis on additional *in vivo* and *in vitro* dermal absorption study data available to EPA at the time to determine the factors (e.g., species, skin residence time before wash-off, dermal loading per skin surface area) that may impact the evaluation of efficiency of the hand rinse and face/neck wipe methods. EPA determined that the AHETF submission was not amenable for a statistical analysis of these factors and did not support reconsideration of EPA's position on the MEA.

To address these concerns, in 2013, the AHETF provided an analysis of "triple pack" datasets – datasets were comprised of 3 studies for each individual pesticide tested: rat *in vivo,* rat *in vitro,* and human *in vitro* dermal absorption studies.[16] The AHETF reviewed 74 reports conducted on a total of 33 active ingredients. The analysis included 28 rat *in vivo*, 39 rat *in vitro*, and 40 human *in vitro* studies with 24 datasets that contained complete triple pack data. Multiple studies were conducted using different formulations of the same active ingredient. However, the AHETF's ultimate proposal was based on analysis from 15 human *in vitro* skin studies that were part of complete triple pack data sets (some data from the original 24 datasets were excluded based on exposure period considerations), as well as an additional 10 human *in vitro* studies, which were not part of complete triple pack datasets.

In this submission, the AHETF documented the various factors that may impact dermal absorption, including species (e.g., humans, rats, etc.), type of study (e.g., *in vivo* or *in vitro*), dermal loading (µg exposure per cm^2 skin), exposure duration (i.e., time-to-removal, wash/wipe-off time, or residence time on skin), and chemical-specific properties. Generally, the "triple pack" approach permits refinement of *in vivo* results using rat skin by correcting for any differences between *in vitro* and *in vivo* absorption rates in the rat as well as for species differences seen between *in vitro* rat skin and *in vitro* human skin. This refinement in dermal absorption is important since absorption by human skin is generally lower than rat skin and so the combined use of the data from three studies and two testing systems offers potential for greater accuracy in estimating human dermal absorption. Subsequent to the 2013 submission (MRID 49173001), the AHETF sent two letters (one in 2014 and one in 2015, both captured under EPA MRID 52028103) and another formal submission in 2022 addressing the impact of the MEA on EPA's Seed Treatment Policy (MRID 52028102). The task force also submitted a follow-up letter to EPA in 2024 (MRID 52321101).

The "triple pack" dermal absorption data collected and submitted by AHETF in 2013 was robust, representing 33 pesticides. EPA agrees that, in the absence of more direct validation of the removal techniques/protocols employed in the studies, the premise of using information from *in vivo* and *in vitro* dermal absorption studies to evaluate removal methods in exposure monitoring studies is appropriate to evaluate the continued use of the MEA. However, EPA noted that the AHETF-submitted dataset included dermal absorption results for only 4 pesticides (carbaryl, chlorothalonil, imidacloprid, and pendimethalin) used in the task force exposure monitoring studies. As dermal absorption can be different across pesticides, it is important to utilize data representative of the pesticides used in the

[16] Canez, V.M. (2013), Assessment of AHETF-member in-vitro Human Skin Dermal Penetration Data to Eliminate the Use of EPA's Default Method Efficiency Adjustment (MEA) Factor for AHETF Worker Exposure Data (AHE301), Sponsor: AHETF. MRID 49173001.

actual exposure monitoring studies in question. Thus, EPA has also reviewed internally and externally available dermal absorption studies to establish a larger set of data, including more data for the pesticides used in exposure monitoring studies as well as more data covering a wider range of factors that could affect dermal absorption.

3.0 Overall Evaluation Approach

Ideally in order to address uncertainty associated with sampling inefficiency of removal-style methods used in exposure monitoring studies, data would come from a test where a known amount of pesticide is applied to a participant's skin followed by a measure of the pesticide removed by the hand rinse and face/neck wipe protocols. A method validation study would provide critical information on the removal efficiency and reproducibility of those methods, and whether an adjustment factor should be required. Absent this kind of study, an alternative approach is to consider other studies/data as a surrogate indicator or analog of collection method efficiency to address this uncertainty.

The AHETF proposed using available laboratory dermal absorption studies as an analog for addressing the removal efficiency of their bare-skin collection protocols. EPA agrees with this approach since the dermal absorption study protocols and the hand rinse and face/neck wipe methods all use aqueous surfactant solutions coupled with some form of mechanical agitation to remove residues on the surface of the skin. In dermal absorption studies, known amounts of pesticide are applied to a standard surface area of the skin (*in vitro* or *in vivo*). The amounts of pesticide applied are expressed as solution concentrations which EPA converted to "dermal loadings" in mass of chemical applied per surface area (e.g., $\mu g/cm^2$), given that the volume of solution applied is known. These amounts are then removed at specific timepoints with an aqueous soap or alcohol solution using a wipe, via rinsing, or via a cotton tip applicator. Post-exposure measurements are also collected using a series of tape strips to determine the amount of material remaining at the skin site after washing and are evaluated as potentially absorbable. Laboratory technicians must be careful not to apply too much force during removal as skin can be abraded or damaged (artificially altering absorption potential). EPA generally considers the amount measured in the first two tape strips (when analyzed separately) to be unabsorbable as these are thought to capture levels of chemical on the outermost layer of the skin which are removed during normal washing activities and desquamation and, therefore, not available for further absorption. The remaining tape strips contain material that is considered as potentially absorbable and was included for this analysis, unless it was concluded in the risk assessment that there were data demonstrating that the chemical will not continue to traverse the skin into systemic circulation. In those instances, skin-associated chemical (e.g., all tape strips) was not included in the dermal absorption calculation. Dermal absorption can then be estimated as the sum of both the absorbed dose (i.e., receptor fluids, percentage measured in excreted CO_2, urine, feces, blood, organs, and carcass) and the potentially absorbed dose (e.g., chemical associated with the skin), when applicable.

In contrast, exposure monitoring study sampling methods direct researchers and participants to scrub their hands while the wash solution is poured over their hands to remove residues which have contacted the skin during a monitoring period. These monitoring study methods may remove more from the skin than in the wash-off of dermal absorption studies because the mechanical agitation involved in wiping the face and neck areas and rinsing the hands are intentionally vigorous. There is

also potential variability in the rigor of the handwashes and face and neck wipes between the individual workers.

Compared to the dermal exposure sampling method, dermal absorption studies are likely less variable and more precise, but likely not as vigorous as the dermal sampling method. Although this might result in underestimation of the actual removal in the monitoring studies, the dermal absorption studies provide a strong and robust database that allows for scientifically sound evaluation of exposure monitoring sampling methods.

A comparison of the specific protocols used for residue removal sampling in exposure monitoring studies as well as in dermal absorption data collection are provided below for informative purposes. Key elements excerpted from the AHETF residue removal sampling SOPs include[17]:

- **SOP AHETF 8.B.9 - Handwash (Sec 3.1):** The desired solution concentration is 0.01% w/v Aerosol® OT (AOT) in water. A sufficient quantity should be made for the projected number of hand washes (500 mL for each hand wash).

- **SOP AHETF 8.B.9 - Handwash (Sec 4.6-4.8):** Have the worker place both hands over a bowl and pour approximately 400 mL of 0.01% Aerosol® OT solution over the worker's hands for approximately 30 seconds. The worker will scrub their hands while the wash solution is slowly poured over the worker's hands. The worker shall then immerse their hands in the 400 mL of the wash solution in the collection bowl and lightly scrub their hands in the solution for a minimum of 30 seconds. The worker should lift their hands out of the wash solution, and while holding their hands over the bowl, the remaining approximate 100 mL of Aerosol® OT is poured over the worker's hands to rinse. Allow the hands to drain for approximately five seconds.

- **SOP AHETF 8.C.7 - Dermal Face/Neck Wipe Procedures (Sec 3.2):** Dispense approximately 4 mL of the surfactant solution (0.01% Aerosol® OT) on the gauze sponge with the syringe or pipette (or other appropriate means of moistening the sponge).

- **SOP AHETF 8.C.7 - Dermal Face/Neck Wipe Procedures (Sec 3.4):** Thoroughly wipe the worker's face/neck (front & back) with the moistened sponge.

Key elements are presented below related to dermal absorption protocols that are widely used. These were excerpted directly from each document:

- **OPPTS 870.7600: Dermal Penetration (pg 5, Section (6)):** At the exposure intervals (0.5, 1, 2, 4, 10 and 24 h for the standard study) four animals per dose are anesthetized, exposed skin is washed with a mild soap/detergent solution followed by several water rinses, to mimic human washing, and the protective device is removed[18]. The skin at the exposure site must be washed before it is removed from the animal. Note – in recent years, EPA has encouraged exposure

[17] Note: other pesticide task forces (e.g., ARTF and ORETF previously mentioned) and monitoring studies used functionally equivalent sampling methods as the AHETF.

[18] From the guideline: "A combination cover (protective device) consisting of a spacer (a rubber, plastic or glass rectangle, square, or ring glued to the skin) to outline the application site and a filter paper or gauze cover glued to it is recommended."

durations of 6 -10 hours with later timepoints for post-application evaluation after the chemical has been rinsed/washed off in lieu of the proposed exposure intervals in the guideline.

- **OECD Guideline For The Testing Of Chemicals, Skin Absorption: *in vivo* Method 427 (4/13/04):** The treated skin of all animals should be washed at least 3 times with a cleansing agent using suitable swabs. Care must be taken to avoid contaminating other parts of the body. The cleansing agent should be representative of normal hygiene practice, for example an aqueous soap solution. Finally, the skin should be dried. All swabs and washings must be retained for analysis.

- **OECD Guideline For The Testing Of Chemicals, Skin Absorption: *in vitro* Method 428 (4/13/04):** The skin should be washed of excess test preparation with a relevant cleansing agent, and the rinses collected for analysis. The removal procedure of the test preparation will depend on the expected use condition and should be justified.

4.0 Available Dermal Absorption Data

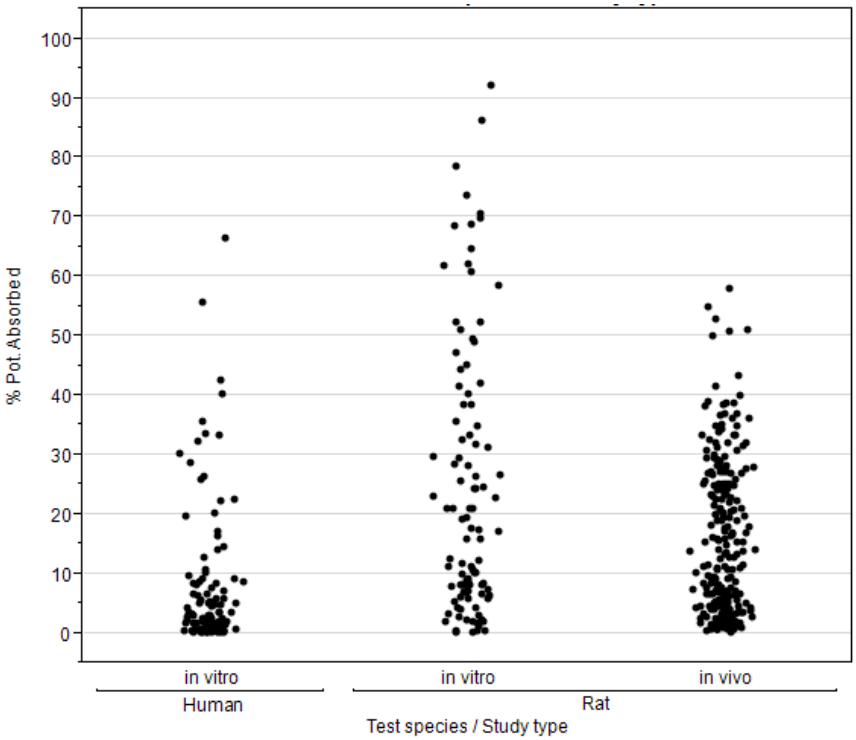
As described below, the approach used in EPA's analysis is similar to that employed in the 2013 AHETF submissions. However, EPA has attempted to collect more available dermal absorption data, both within the U.S. and internationally, to review data for specific chemicals used in the exposure monitoring studies, as well as ensure that this evaluation relies on a comprehensive dataset that covers a broad range of potential factors that can affect dermal absorption.

4.1 AHETF 2013 MEA Report and Dermal Absorption Data

The AHETF asked their member companies to submit company-sponsored dermal absorption studies, which were then compiled and submitted to EPA in 2013 along with a report about how the results of those studies can help characterize the MEA. The AHETF submitted data from 74 dermal absorption reports (some containing multiple datasets) representing triple pack studies for 33 different active ingredients. As is typical, all animal study data were conducted in rats. Exposure durations (i.e., wash-off times) in the original dataset ranged from 0.5 to 120 hours for *in vivo* studies and 6 to 48 hours for *in vitro* studies. However, AHETF only included data where the exposure period was ≤ 10 hours in the *in vivo* studies and ≤ 8 hours in the *in vitro* studies. Dermal loadings ranged from 1 to 6180 µg/cm^2 for rat *in vivo* studies and 0.05 to 5810 µg/cm^2 for rat and human *in vitro* studies. All studies were conducted under the OPPTS/OECD standard guidelines previously mentioned.

Figure 2 below provides a graphical summary of percent potentially absorbed across all the AHETF 2013 data – for simplicity, the data are categorized into species (rat and human) and study type (*in vivo* and *in vitro*). The average dermal absorption across all the submitted human *in vitro* data from a variety of pesticides was < 10%, inversely indicating > 90% of the administered pesticide was collected at the wash-off time (analogous to the residue removal by the hand rinse and face/neck wipe methods in exposure monitoring studies). As a result, the AHETF stated that the hand rinse and face/neck wipe methods should be regarded as having near-complete recovery of residues from monitoring study participants' skin surfaces and that the MEA can be removed from applicable datasets. However, the EPA chose to review additional available dermal absorption data as described below.

Figure 2. AHETF 2013 "Potentially Absorbed (%)" Plotted by Species Type and Study Type



4.2 Dermal Absorption Data Submitted to EPA for Pesticide Registrations

While the AHETF 2013 submission provided robust dermal absorption information across 33 active ingredients, EPA found that only 4 of the 33 active ingredients represented in the dataset were pesticides used in the exposure monitoring studies. As the efficiency of the hand rinse and face/neck wipe methods are partially dependent on the specific pesticide used in the monitoring studies, having comparative dermal absorption data for those specific chemicals would be useful. Therefore, EPA chose to conduct an additional review of available dermal absorption data specifically for the pesticides used in exposure monitoring studies. As dermal absorption data is routinely submitted to EPA for registration purposes, EPA potentially has a broader dataset available than what was available to the AHETF.

EPA first reviewed all exposure monitoring study data used in U.S. pesticide regulatory assessments to determine relevant pesticide chemicals of interest. While the MEA was developed in the context of AHETF research, data from other sources (e.g., ARTF, ORETF, and data sources referenced in the Residential SOPs) were reviewed for the identity of monitoring study pesticides for which dermal absorption data might be available. After reviewing each exposure data source, a total of 47 distinct pesticides, across multiple formulations, were identified as having been the subject chemical in an exposure monitoring study that underlies a major EPA pesticide assessment data source. Table 3 provides a summary of the 47 chemicals, including the database in which it is housed, and the frequency of use within monitoring studies. Note that daily monitoring events are referred to as "monitoring units (MUs)", a term used to refer to monitoring of an individual doing a specific task

during a single monitored period. In other words, if an individual is monitored for 3 separate tasks throughout the day it would result in 3 separate MUs.

Table 3: Chemicals Used By Various Exposure Task Forces And In Individual Studies Included In Residential SOPs Not Generated By A Task Force

Chemical #	Chemical/Active Ingredient (AI)	Used As A Surrogate ("X") & # Monitoring Units (n)[1,2,3]		
		AHETF	ARTF	ORETF/ ResSOPs
1	2,4-D	X (13)		XX*(40)
2	2,4-DB	X		
3	Acephate	X (18)		XX*(18)
4	Azoxystrobin	X (7)		
5	Captan		X (40)	
6	Carbaryl	X (29)	X (141)	XX (220)
7	Chlorothalonil	X (78)	X (188)	XX (20)
8	Chlorpyrifos	X (1)	X (8)	
9	Cyfluthrin		X (15)	
10	DCPA (Dacthal)	X		X (170)
11	Diazinon	X (5)	(15)	X (60) XX (33)
12	Diquat			XX (20)
13	Disulfoton			XX (60)
14	Dithiopyr	X		X (80)
15	Ethalfluralin	X		
16	Fipronil			XX*(42)
17	Fluvalinate			XX (0)
18	Fosamine ammonium	X (3)		
19	Fosetyl-al	X (1)		
20	Glyphosate	X (55)		XX (20)
21	Hexazinone			XX (129)
22	Imazapyr	X (13)		
23	Imidacloprid	X (13)		
24	Malathion	X (35)	X (145)	
25	Mefenoxam (metalaxyl)	X (2)		
26	MGK 264			XX (16)
27	Naled		X (10)	
28	Napthalene			XX*(3)
29	Oryzalin			XX (15)
30	Pendimethalin	X (4)		
31	Permethrin	X		
32	Prallethrin			XX (0)
33	Profenofos		X (29)	
34	Propargite		X (93)	
35	Propazine	X		
36	Propoxur			XX (15)
37	Pyrethrin			XX (20)
38	Piperonyl butoxide			XX (20)
39	Simazine	X (32)		
40	Sulfur	X (19)		
41	TCVP			XX (25)
42	Tefluthrin	X		
43	Thiophanate-Methyl	X (12)		
44	Triadimefon		X (20)	

Table 3: Chemicals Used By Various Exposure Task Forces And In Individual Studies Included In Residential SOPs Not Generated By A Task Force

Chemical #	Chemical/Active Ingredient (AI)	Used As A Surrogate ("X") & # Monitoring Units (n)[1,2,3]		
		AHETF	ARTF	ORETF/ ResSOPs
45	Tribufos	X (23)	X (25)	
46	Triclopyr			XX (20)
47	Vinclozolin		X (38)	

1. If "X" is shown with no (value), the chemical was a potential surrogate active ingredient for the included exposure studies but was never used by a study participant.
   If a * is included, skin residue removal sampling methods were not used in the applicable study.
   If "0" is reported, then the study was rejected for science or ethics concerns, but the dermal absorption data was still included in this analysis to provide a range of information.
2. For ORETF/ResSOPs column, "XX" indicates individual handler exposure monitoring studies referenced in the Residential SOPs but not a ORETF sponsored study (denoted with "X").
3. Data for Seed Treatment submitted by the AHETF are not included in this table. However, approximately 30% of that data is comprised of participants using imidacloprid, metalaxyl, acephate, and tefluthrin which are included in this table.

For each of the 47 pesticides, the most recent regulatory risk assessments were reviewed, and pertinent dermal absorption information was extracted across 76 studies and compiled into a spreadsheet (data file "AppA_OPP_MEA_Response_010821.xlsx" provided in Appendix A), including:

- Risk assessment document identifiers
- Dermal toxicological endpoint information including:
  - Applicable exposure scenario
  - Point of departure
  - Applicable uncertainty factors
  - Study type (species, route of administration, identifiers, results)
- Dermal absorption information including:
  - Study identifiers
  - Absorption factors determined in each study
  - Test species used (animal or human)
  - Results (loading rates, sample methods, time course data, etc.)

As previously described, the focus of this effort to evaluate the MEA relies specifically on dermal absorption data as analogous to the removal of residues by the hand rinse and face/neck wipe protocols for exposure monitoring studies. Dermal absorption information was found for 35 of the 47 chemicals identified in Table 3 plus data for one key environmental degradate. The remaining 12 chemicals did not have any dermal absorption data referenced in their most recent risk assessments. Of the 35 chemicals with dermal absorption information, 29 chemicals had data useful for a full analysis. Exclusions of data was usually based on lack of information related to a specific field such as mass balance results or skin residue removal efficiency values. Each dataset, or packet of information, reflects the data as reported in the original research and typically represents compiled values from several replicated measures within a particular test condition (e.g., mean results for multiple animals necropsied at a particular time at the same dose level). The information which was collected from each study included the following data fields:

- Chemical # (see Table 3 above)
- Study reference
- Study #
- Chemical ID
- Dermal loading of test material based on active ingredient (µg/cm^2)
- Dose rate (total mg active ingredient applied)
- Test species
- Study type (i.e., *in vitro* or *in vivo* study protocol)
- Flux if available, units varied by study and are reported individually
- Exposure duration or wash times (hours, focused on initial wash time if sequential washes occurred)
- Collection times (usually at necropsy)
- Mass balance (Total % recovery of known amount initially applied)
- Dermal absorption value (% of total applied, calculated as absorbed plus potentially absorbed, when applicable)
- Removal from skin surface (% of total applied, i.e., unabsorbable fraction)
- Information on mass balance and removal from skin methods (i.e., washing or swabbing)

The species and study type are summarized below for the 531 datasets EPA compiled from the 29 chemicals that had data useful for a full analysis (# datasets, % of total data):

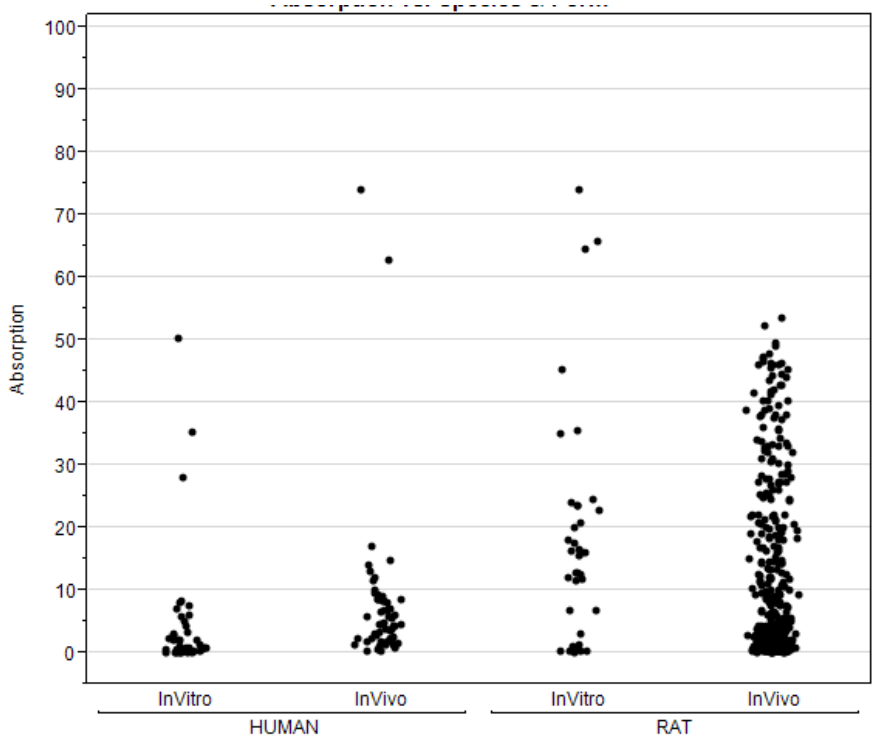
- Human *in vitro* (47, 8.85%)
- Human *in vivo* (14, 2.64%)[19]
- Monkey *in vivo* (3, 0.56%)
- Porcine *in vitro* (1, 0.19%)
- Rabbit *in vitro* (6, 1.13%)
- Rat *in vitro* (41, 7.72%)
- Rat *in vivo* (419, 78.91%)

Exposure durations (i.e., wash-off times) ranged from 0.25 to 144 hours for *in vivo* studies and 6 to 48 hours for *in vitro* studies. While exposure durations of ≤24 hours are preferred for *in vitro* studies, the longer exposure durations were included which may result in a more conservative analysis. Treatment doses ranged from 0.3 to 5000 µg/cm^2 for animal *in vivo* studies and 0.7 to 40200 µg/cm^2 for animal and human *in vitro* studies.

Figure 3 below provides a graphical summary of percent absorption across all this data – for simplicity, the data is categorized into species (rat and human, specifically) and study type (*in vivo* and *in vitro*). The data is distributionally similar to the AHETF 2013 submission (Figure 2 above) and the average dermal absorption across all data (species and study type) collected by EPA was also approximately 10%.

[19] This data review contained data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These human *in vivo* dermal absorption studies are, (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements.

Figure 3. Available EPA Dermal Absorption Data Plotted by Species Type and Study Type



4.2.1 Initial Data Analysis of Dermal Absorption Data Submitted to EPA

The AHETF's ultimate proposal was based on analysis from 15 human *in vitro* skin studies that were part of complete triple pack data sets, as well as an additional 10 human *in vitro* studies, which were not part of complete triple pack datasets. The AHETF concluded that the human *in vitro* wash off fraction would be a suitable predictor for human health risk assessments by comparing the rat *in vitro* / *in vivo* dermal absorption ratios, that indicated the rat *in vitro* dermal absorption data are suitable predictors of the *in vivo* dermal absorption, and applying the same concept to the human *in vitro* studies.

The EPA decided to conduct an initial analysis of the dermal absorption data submitted to EPA through pesticide registrations as detailed in the previous section (4.2). EPA's initial analysis modeled all data in the available dermal absorption studies received disregarding any differences in species (i.e., human and rat) and study type (i.e., *in vitro* and *in vivo*). Data were also available for monkey, mouse, porcine, and rabbit, but due to the small sample sizes for these species, only rat and human data were analyzed. After cleaning the data (i.e., replacing absorption = 0% with absorption = 0.01% for some datapoints; deleting records with missing absorption, loading rate, wash time (i.e., exposure duration), and/or information on *in vitro* vs *in vivo*), there was a total of 569 datapoints from rat and human studies (44 human – *in vitro*, 57 human – *in vivo*, 38 rat – *in vitro*, and 430 rat – *in vivo*). With dermal absorption being expressed as a fraction or percentage of exposure absorbed (skewed towards low percent dermal absorptions and bounded between minimum possible = 0% and maximum possible = 100%), logit-transformation of dermal absorption percentage was used to facilitate statistical analysis and modeling to achieve normality of errors and avoid the possibility of nonsensical negative predicted values from the models.

As mentioned in comments regarding AHETF's initial submission, EPA's initial analysis focused on the impact of dermal loading (µg/cm^2) and exposure time (i.e., on-skin "residence time"). A mixed-effects model analysis was used to evaluate the association between percent of dermal absorption and loading for both human and rat study data. Dermal loading was significantly and negatively associated with the percent absorption (p-value < 0.001) and exposure duration was significantly and positively associated with the percent absorption (p-value < 0.001). The figures below visually demonstrate the negative relationship between percent of dermal absorption with loading, i.e., percent of absorption decreases as dermal loading increases and the positive relationship with exposure duration, i.e., percent of absorption increases as exposure time increases. The figures present the same model however Figure 4 displays the logit-transformed data and Figure 5 displays the un-transformed data.

Figure 1. EPA's Initial Analysis – Model Predicted logit Dermal Absorption Values Across Dermal Loading

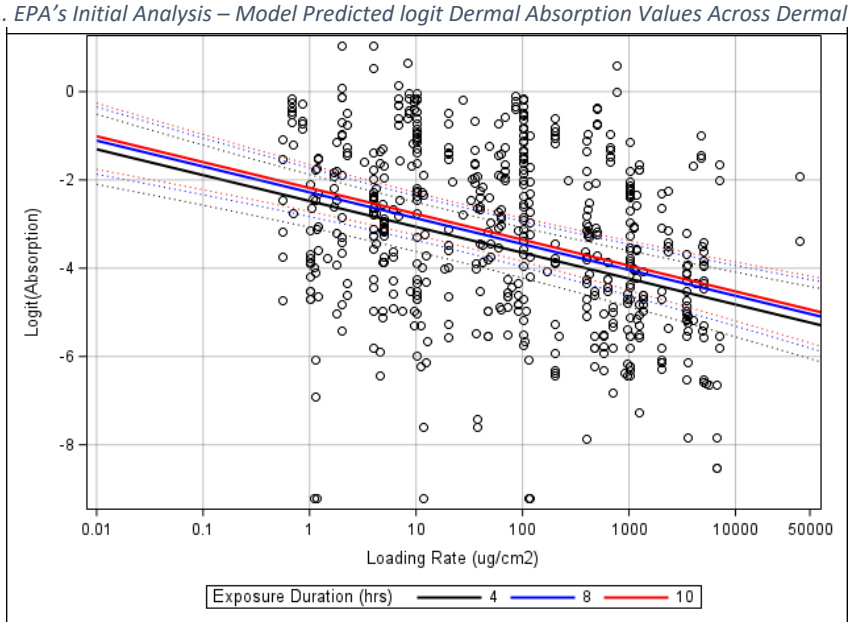
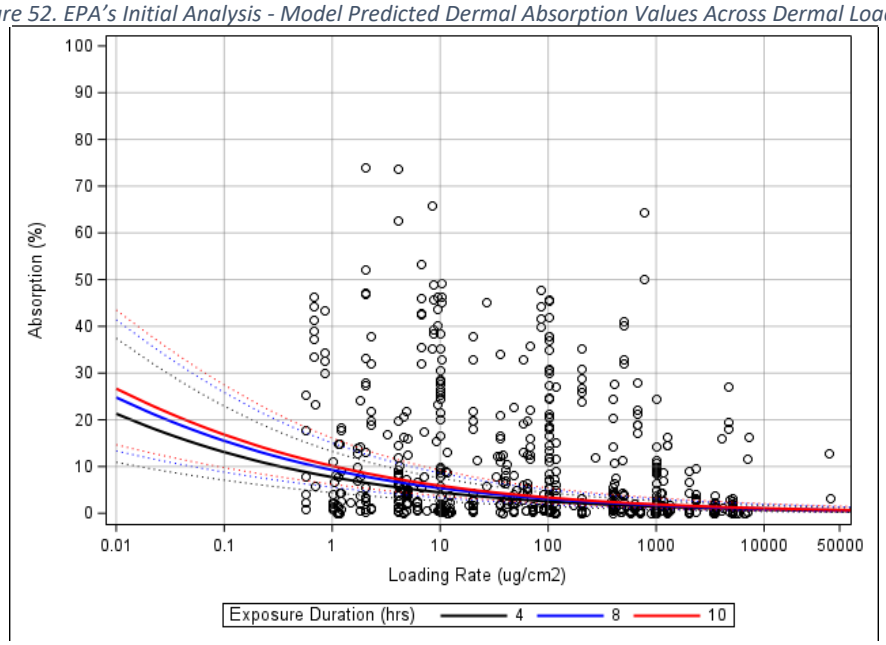


Figure 52. EPA's Initial Analysis - Model Predicted Dermal Absorption Values Across Dermal Loading



Following this initial analysis, which did not differentiate between species or study type, EPA further considered the impact of several variables on dermal absorption. These included:

- Exposure duration
- Dermal Loading
- Species (rat or human)
- Study type (*in vivo* or *in vitro)*

Exposure Duration

When considering exposure duration, EPA agrees with the AHETF that exposure periods of ≤10 hours in dermal absorption studies are most relevant to worker exposure studies, so further analyses do not focus on studies with long exposure times. Generally, the sampling period between hand wash samples in worker monitoring studies is less than 8 hours, and commonly 4 hours or less, depending on the exposure scenario (i.e., multiple hand wash samples in a given workday).

Dermal Loading

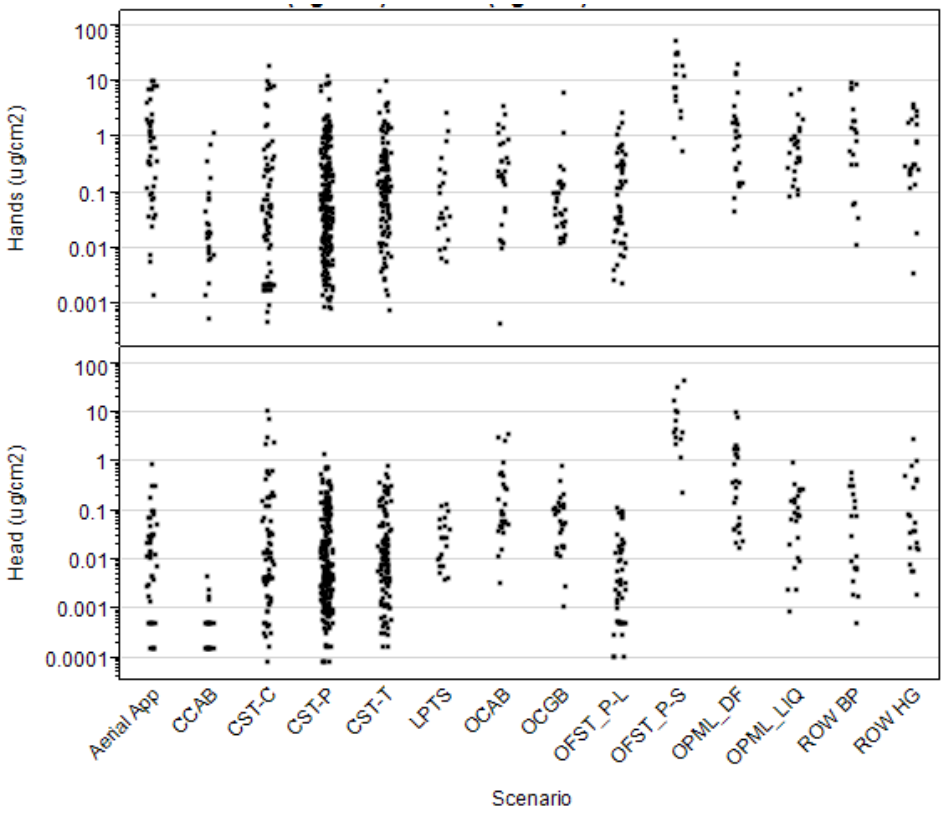
Dermal loading (µg exposure per cm^2 skin) is a more complicated variable to consider. Ultimately, from the collected worker monitoring samples, only the *total daily measured* exposure is known, not exposure or dermal loading at discrete time points. Body part surface areas, on the other hand, are reasonably well known from historical publications (e.g., EPA's Exposure Factors Handbook (EFH))[20]. Thus, simple division will provide an estimate of the *measured* dermal loading in mass of chemical per square centimeter of skin. Two important unknowns, however, are: a) the timing of exposure – that is, whether the total daily exposure happened in a single exposure event, or is a cumulative total from a series of events over the course of the monitoring period, and b) the distribution of the mass of chemical over the body part – that is, whether the amount is evenly distributed over the body part or

[20] Chapter 7 of the EPA's Exposure Factors Handbook (EFH) available at: https://www.epa.gov/expobox/about-exposure-factors-handbook

whether it is concentrated on a smaller area. Both unknowns can have a significant effect on estimates of dermal loading, which, as seen above is an important variable for absorption potential.

Without further information on these unknowns, the known daily samples and body part surface area estimates can be used to provide reasonable estimates of the measured dermal loadings. As the MEA is focused on the hands and head – body parts whose exposure is collected via skin residue removal techniques (not interception techniques) – approximate surface areas, recommended in the EFH, are used to estimate dermal loading: 1070 cm^2 for hands and 910 cm^2 for the face and neck. For the dermal loading evaluation, data from AHETF was extracted as it is the most relevant for application of the MEA. Exposures for hands were normalized by 1070 cm^2 and for face/neck by 910 cm^2 to produce Figure 6 below. These represent exposures across many scenarios such as applications with tractors and handheld applications in greenhouses. The data is categorized by exposure scenario for additional clarity (data file provided in Appendix A.1).

Figure 63. Observed Dermal Loadings of the Hands (µg/cm^2) and Head (µg/cm^2) Across Worker Scenarios



Aerial App = aerial applications; CCAB = closed-cab airblast; CST-C = commercial seed treatment, cleaning equipment; CST-P = commercial seed treatment, packaging seed; CST-T = commercial seed treatment, treating seed; LPTS = loading and planting treated seed; OCAB = open-cab airblast; OCGB = open-cab groundboom; OFST_P-L = on-farm seed treatment and planting, liquid formulations; OFST_P-S = on-farm seed treatment and planting, solid formulations; OPML_DF = open pour mixing and loading, dry flowables; OPML_LIQ = open pour mixing and loading, liquids; ROW BP = rights-of-way applications with backpack sprayer; ROW HG = rights-of-way applications with handgun sprayer.

This analysis of measured dermal exposure, converted to best-estimates of dermal loading (Figure 6 above), indicated that loading rates on the skin can be very low. While dermal absorption results at higher dermal loadings are helpful to construct an overall model (see Figures 4 and 5 above), it may be

that higher dermal loadings are not as reflective in terms of assessing potential dermal absorption for actual exposures in the field. In fact, judging the efficiency of bare skin removal methods based on dermal absorption results at very high dermal loadings could be misleading. Thus, the lack of "low-end" dermal loading representation in the EPA-only data was additionally noted in our initial analysis.

Species and Study Type
As noted above, the initial analysis did not differentiate species (rat or human) or study type (*in vivo* or *in vitro*). However, upon analysis the percent absorption of rat was determined to be significantly higher than human (p-value < 0.001) as expected given known skin differences between species that result in greater permeability of rat skin (e.g., increased density of hair follicles and decreased thickness of rodent skin relative to human skin). Due to these species differences, the EPA considered additional modeling by further separating these variables, with a preference for human *in vitro* data. However, the EPA-only data is limited in the amount of human *in vitro* results, as shown in Figure 3. Additionally, the available human *in vitro* data does not contain dermal loading rates in the lower range, which EPA identified as a potential limitation above. Therefore, additional publicly-available dermal absorption data was identified in the open literature to potentially augment the available EPA-only data.

4.3 Dermal Absorption Datasets Available in Published Literature

The data collected by EPA from its in-house registration submissions process appropriately focused on the specific chemicals measured using the hand rinse and face/neck wipe methods in question. However, EPA also reviewed publicly available literature for additional data sources that might augment the data further, for example by providing more human-specific data or capturing more of the range of variability in factors that influence dermal absorption. Two additional peer-reviewed publicly available datasets were identified: Allen, et al., 2021[21] and EFSA, 2017[22]. We note here some limitations on using these datasets, particularly that each individual study comprising the datasets has not been fully reviewed internally by EPA. That said, the data is described by the sources as having followed OECD Guidelines – similar to data submitted to EPA, which typically follows OCSPP Test Guidelines. Both are subject to a level of peer review before being made publicly available. Furthermore, as the same dermal absorption studies can be submitted to various countries, it could be the case that some of the same data is duplicated within this analysis. We did not, however, notice any obvious trends with respect to this potential issue. Despite these limitations, the use of as large a dataset as possible is reasonable, particularly as the additional data augments human absorption and dermal loading data gaps observed in EPA's existing dataset.

Allen, et al., 2021 was an effort by the U.S. EPA and U.S. research facilities to conduct a retrospective analysis of pesticide dermal absorption data submitted to EPA to evaluate the utility of *in vitro* dermal absorption studies alone against the standard "triple pack" approach (i.e., *in vivo* animal studies accompanied by *in vitro* human and animal studies). The authors concluded that the *in vitro* rat

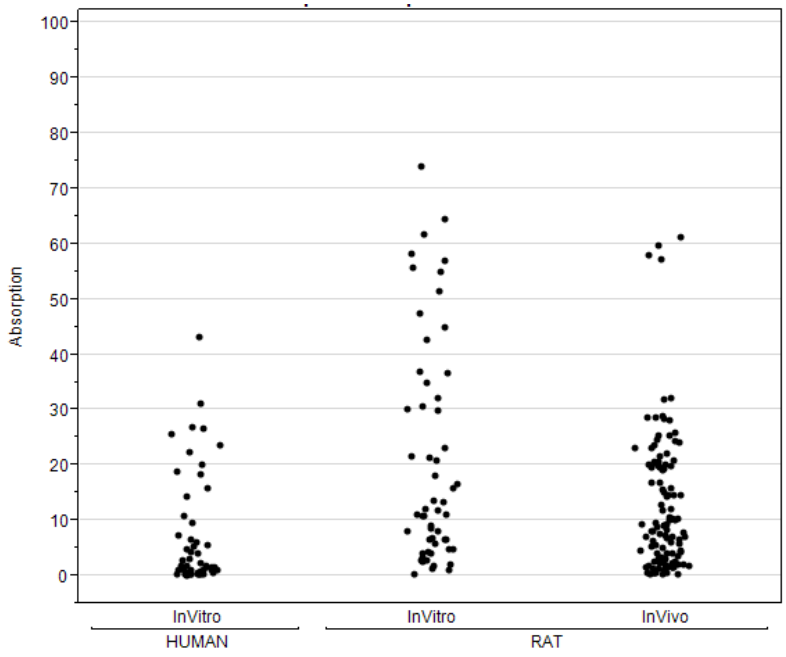
[21] Allen DG, Rooney J, Kleinstreuer N, Lowit A, Perron M. Retrospective analysis of dermal absorption triple pack data. ALTEX. 2021;38(3):463-476. doi: 10.14573/altex.2101121. Epub 2021 Mar 12. PMID: 33712859. Also here: https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/ocular/dermasorb

[22] EFSA (European Food Safety Authority), Buist, H, Craig, P, Dewhurst, I, Hougaard Bennekou, S, Kneuer, C, Machera, K, Pieper, C, Court Marques, D, Guillot, G, Ruffo, F and Chiusolo, A, 2017. Guidance on dermal absorption. *EFSA Journal* 2017; 15(6):4873, 60 pp. https://doi.org/10.2903/j.efsa.2017.4873

method generated a similar or higher dermal absorption percentage than the *in vivo* method and that the human *in vitro* method provided a similar or higher estimate of dermal absorption than the triple pack approach. Therefore, the authors concluded that the analysis supports potentially using *in vitro* data alone for dermal absorption derivation for human health risk assessment of pesticides.

Importantly, Allen, et al. (2021) publicly provided the dermal absorption data used for their analysis,[23] providing an additional dataset that can augment the data collected by EPA from its in-house registration submissions process, in particular, by doubling the amount of human *in vitro* data available for analysis. The data was downloaded and is provided in Appendix A. Exposure durations (i.e., wash-off times) ranged from 6 to 10 hours for both *in vivo* and *in vitro* studies. Dermal loadings ranged from 0.25 to 8000 µg/cm^2 for rat *in vivo* studies and 0.225 to 8000 µg/cm^2 for animal and human *in vitro* studies. While Allen, et al. (2021) were unable to publish study or chemical identifiers (making cross-checking duplicative data difficult to determine), the additional human-specific (*in vitro*) data is valuable for the current EPA analysis. Figure 7 below provides a graphical summary of percent absorption across all the Allen, et al. (2021) data. Like other figures presented, the data is categorized into species (rat and human, specifically) and study type (*in vivo* and *in vitro*). The data is distributionally similar to the other datasets presented above, and the average dermal absorption across species and study type in the Allen, et al. (2021) data was approximately 13%.

Figure 74. Allen, et. al. Dermal Absorption Data Plotted by Species Type and Study Type



The European Food Safety Authority (EFSA) published their *Guidance on dermal absorption* in 2017 accompanied by a publicly available dataset.[24] The data was downloaded from that source and is provided in Appendix A. This effort was a comprehensive look at dermal absorption studies to provide

[23] Allen, D., et al., 2021, Retrospective Analysis of Dermal Absorption Triple Pack Data, ALTEX *38(3),* 463-476, https://doi.org/10.14573/altex.2101121; https://pmc.ncbi.nlm.nih.gov/articles/PMC12508965/ https://ntp.niehs.nih.gov/iccvam/methods/ocutox/dermal-data/triplepackfinal-allen2021-508.xlsx

[24] https://zenodo.org/records/3378822#.XosfonduLIF

European stakeholders guidance on conducting dermal absorption studies as well as options for European risk assessors when dermal absorption data is unavailable. The database available for the 2017 guidance focused specifically on human *in vitro* studies (conducted under the OECD guidelines outlined previously) and is comprised of a large amount of data: more than 1000 human *in vitro* data points across 193 pesticides (including 9 pesticides from Table 3), compared with only about 50 human *in vitro* data points each for the EPA and Allen, et al. (2021) datasets previously described.

For the EFSA human *in vitro* data, exposure durations (i.e., wash-off times) ranged from 6 to 24 hours and dermal loadings ranged from 0.04 to 9400 µg/cm^2. Figure 8 below provides a graphical summary of percent absorption across all the EFSA data. The data is distributionally similar to the other human *in vitro* datasets presented above. The overall average dermal absorption in the EFSA data was approximately 10%.

Figure 85. EFSA Human in vitro Dermal Absorption Data Plot

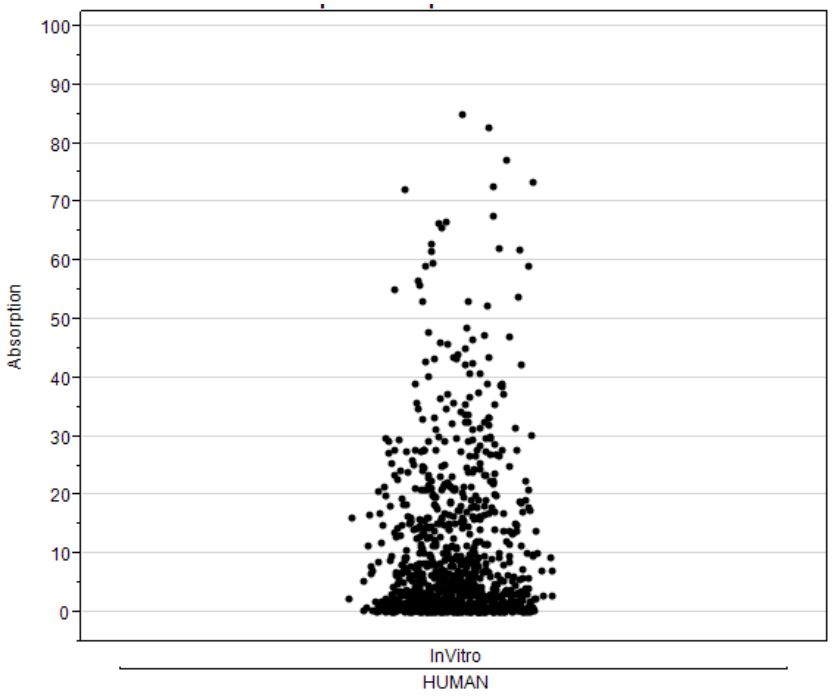


Table 4 below summarizes the available dermal absorption data sources that are described above.

Table 4. Summary of Available Dermal Absorption Data Sources

Data Source	Wash-off times (hours)	Treatment Doses (µg/cm^2)	Dermal Absorption Range (Min – Max)	Average Dermal Absorption
AHETF 2013 MEA Report	0.5 – 120 (*in vivo)* 6-48 (*in vitro)*	1-6180 (rat *in vivo)* 0.05 – 5810 (rat and human *in vitro)*	<1% - 70.6%	<10%

Table 4. Summary of Available Dermal Absorption Data Sources					
Data Source		**Wash-off times (hours)**	**Treatment Doses (µg/cm²)**	**Dermal Absorption Range (Min – Max)**	**Average Dermal Absorption**
Dermal Absorption Data Submitted to EPA for Pesticide Registrations		0.25 – 144 (*in vivo)* 6 – 48 (*in vitro)*	0.3 – 5000 (animal *in vivo)* 0.7 – 40200 (animal and human *in vitro)*	<1% - 74%	~10%
Dermal Absorption Datasets Available in Published Literature	Allen, et. al., 2021	6 – 10 (*in vivo* and *in vitro)*	0.25 – 8000 (rat *in vivo)* 0.225 – 8000 (animal and human *in vitro*)	<1% - 74%	~13%
	EFSA, 2017	6 – 24 (human *in vitro)*	0.04 – 9400 (human *in vitro)*	<1% - 85%	~10%

5.0 Data Analysis

The previous section described the large amount of dermal absorption data compiled to get a broad idea of the range of dermal absorptions. As previously described, dermal absorption is being used as an analog for estimating how much of the total exposure to a worker's hands and face/neck may be missed using current sampling methods. Across all the data and variables considered – all chemicals, species, study type, dermal loadings, exposure/wash-off times – dermal absorption on average was approximately 10%. This suggests that the hand rinse and face/neck wipes are not at risk of "missing" a participant's potential exposure due to significant dermal absorption, and the MEA is potentially unnecessary. However, as seen in Figures 2-8 and Table 4, there is considerable variability in the dermal absorption data (e.g., some of the results are much higher than the overall average result of 10% absorption). This section aims to provide a deeper analysis that further informs considerations for application of the MEA.

First, given existing knowledge about differences between human and rat skin (e.g., as noted in Allen et al., 2021), this section focuses solely on analysis of human data. For obvious reasons related to experimental testing, human *in vitro* data was much more prevalent than human *in vivo* data, however, the human *in vivo* data found in EPA's internal database was also analyzed and included in Appendix A.

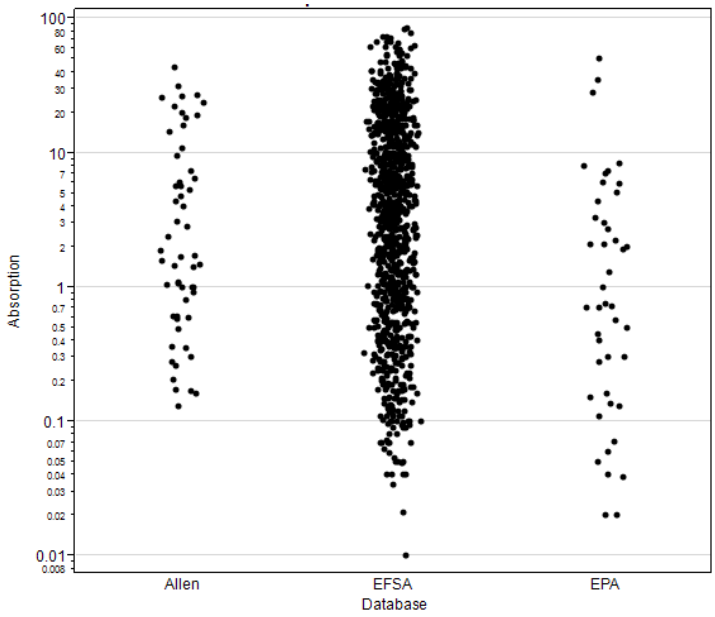
Second, during data review, EPA observed that the human *in vitro* studies from the AHETF 2013 submission are also present in the EFSA database,[25] therefore, to avoid data duplication, only the EFSA database is used, as it subsumes the data in the AHETF 2013 submission.

Third, EPA's internal registration-related data search (Section 4.2 above) focused on pesticides that were specifically the subject of exposure monitoring studies. This was done in case the dermal absorption for those particular pesticides used in exposure monitoring studies is somehow systematically different than pesticides in general. As Figure 9 shows below, it does not appear that the human *in vitro* data compiled by EPA is systematically different than that from Allen, et al. (2021) and EFSA – the datasets all largely cover the same range of dermal absorptions. Thus, given that all studies

[25] As many pesticide companies are global companies, data is often submitted to both the U.S. EPA and EFSA, hence it is unsurprising that the EFSA database also contains data submitted to EPA by the AHETF (a U.S.-based entity).

were conducted under the same OPPTS/OECD Guidelines/Protocols and results were compiled similarly (e.g., including or excluding skin associated chemical as described above), combining all 3 data sources into one dataset provided a significantly robust human *in vitro* dermal absorption dataset.

Figure 96. Human in vitro Dermal Absorption Data Plotted Across Three Datasets



Simple statistics for the combined human *in vitro* dataset, in Figure 10 below, are similar to those for each individual dataset: the range spans from a very small percent absorption to greater than 80%, with a median of about 4% and a mean and 75th percentile of approximately 10%. Again, this might suggest that – due to potentially low dermal absorption – the hand rinse and face/neck wipe methods are not at risk of "missing" any exposure due to significant dermal absorption, and the MEA is potentially unnecessary.

Figure 107. Combined Human in vitro Dermal Absorption Data Plot

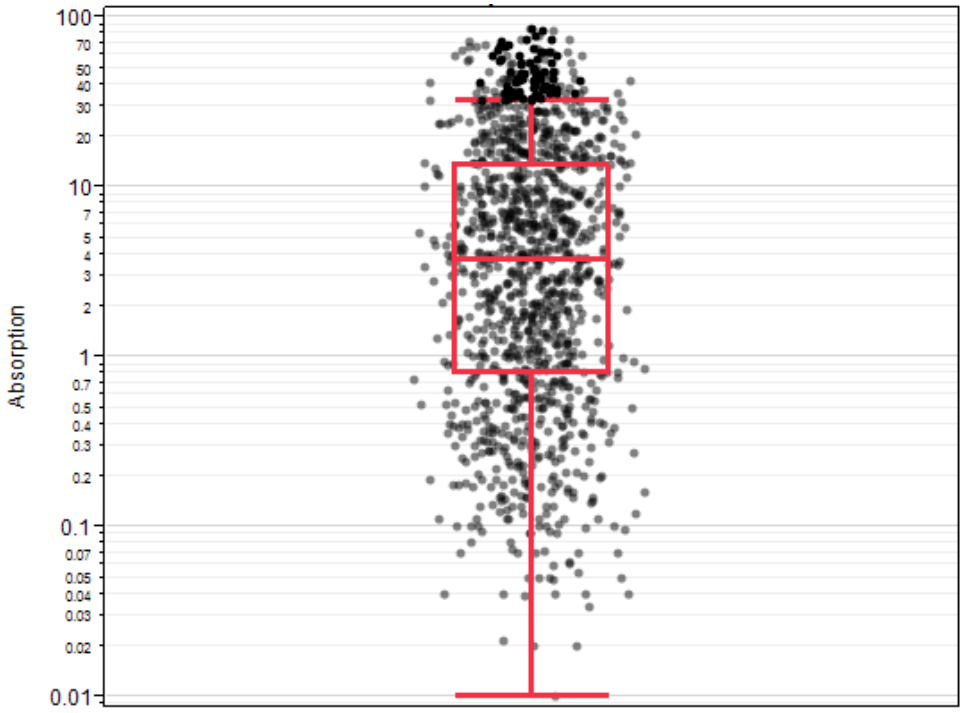


Figure 10 depicts a box plot of the *in vitro* absorption data on a logarithmic scale. The vertical line within the box represents the 50th percentile (i.e., median) and the lower and upper ends of the box represents the 25th percentile (1st quartile) and the 75th percentile (i.e., 3rd quartile), respectively. The difference between the 75th and 25th percentile (i.e., the length of the box) is called the interquartile range (IQR). The whiskers indicate the highest and lowest values within (1.5 x IQR) of the end of the box [i.e., 75th percentile + (1.5 x IQR) and 25th percentile – (1.5 x IQR)].

While overall statistics might ultimately prove useful, this analysis is focused on the reliability of the hand rinse and face/neck wipe methods under the conditions most relevant to the exposure monitoring studies. Therefore, it is important to examine various factors in the dermal absorption studies and their relevance within the exposure monitoring studies. This analysis focused on two factors in the dermal absorption studies that are relevant in exposure monitoring studies: dermal loading per skin surface area (mass chemical/cm^2) and the exposure duration or residence time of the chemical on the skin (i.e., wash-off time). All else equal, it is expected that a longer exposure duration will result in higher fractional absorption (expressed as a fraction of the total applied). Similarly, all else equal, it is expected that higher dermal loadings will have a lower fractional absorption than smaller dermal loadings (when expressed as a fraction of the total applied). Both of which were statistically observed in EPA's initial analysis described above. With this large dataset, we can evaluate the sensitivity of these variables and, to the extent they significantly influence dermal absorption, can then focus judgment on a subset of the data based on corresponding levels within the exposure monitoring studies.

The figures below provide a visual of the human *in vitro* dermal absorption in comparison to exposure duration (i.e., time until wash-off; in hours) and then in comparison to dermal loading (µg/cm^2). The combined dataset of all three databases provides a good range across these variables. In addition, each plot also provides visual characterization of the contribution to the range from each database. Figure

11 shows that most of the dermal absorption data reflects exposure durations of about 10 hours or less which is a close match for potential expected worker exposure durations; however, some data is available to help evaluate longer exposure times (e.g., 24 to 48 hours).

Figure 118. Human in vitro Dermal Absorption Data Plotted by Exposure Durations (hours)

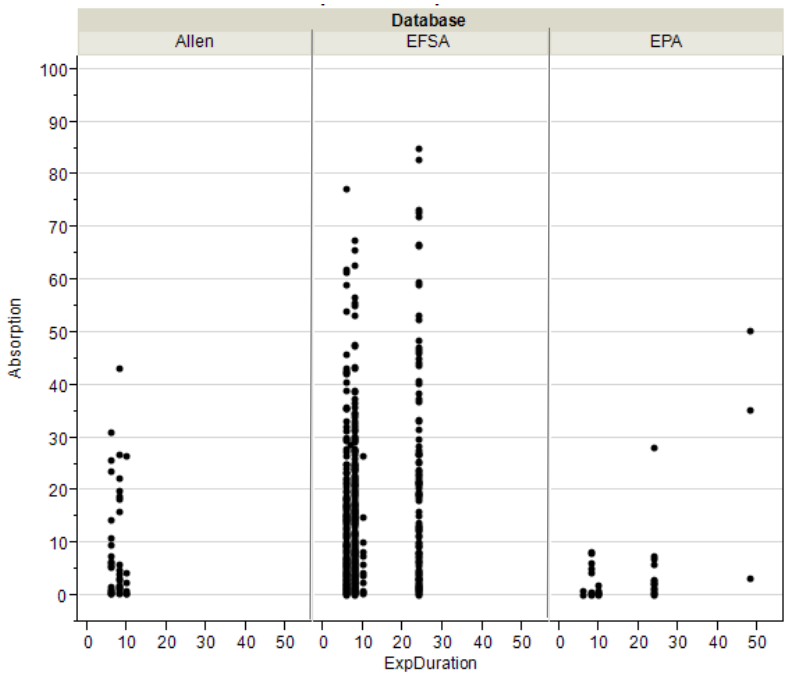
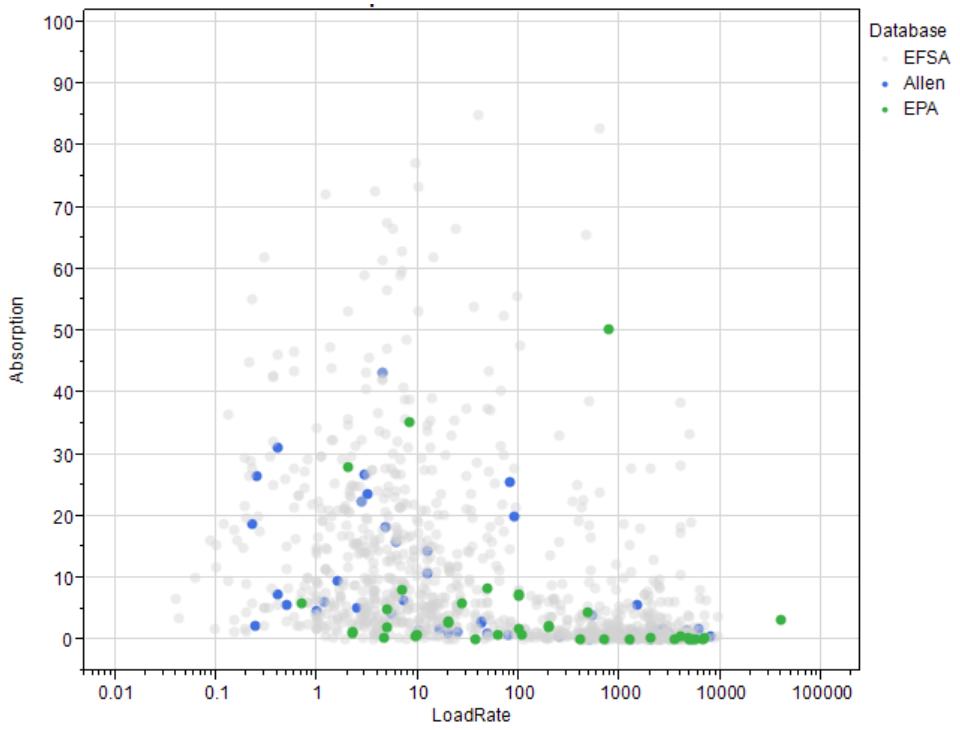


Figure 12 depicts dermal absorption in relation to dermal loading, showing available data with a range of about 5 orders of magnitude. While all datasets generally span the full range, data from both EFSA and Allen, et al. (2021) provide more results from low-end dermal loading than the EPA dataset. With the EFSA dataset containing such a large number of points, the light gray color was used to help visualize each sub-source more clearly.

Figure 129. Human in vitro Dermal Absorption Data Graphed in Relation to Dermal Loading



5.1 Statistical Analysis and Modeling

As described in more detail in Appendix A, dermal absorption was analyzed as a function of exposure duration and dermal loading. While analyses were conducted comparing animal (rat) and humans, as well as *in vivo* versus *in vitro*, the focus in this section, for summary purposes, is on the combined human *in vitro* dataset. As previously stated, given that the *in vitro* studies are conducted under the same protocol and Figure 9 above does not visually indicate anything systematically different across the databases, a combined human *in vitro* dataset provides the most robust and relevant dataset.

With dermal absorption being expressed as a fraction or percentage of exposure absorbed (severely left skewed and bounded between minimum possible = 0% and maximum possible = 100%), logit-transformation of dermal absorption percentage was used to facilitate statistical analysis and modeling to achieve normality of errors and avoid the possibility of nonsensical negative predicted values from the models. Similarly, given its skewed nature, natural log-transformation was used for loading rate, while exposure duration was not transformed. Figures 13 and 14 below recreates Figures 11 and 12 above using the aforementioned transformations.

Figure 1310. Transformed Human in vitro Dermal Absorption Data Plotted by Exposure Durations

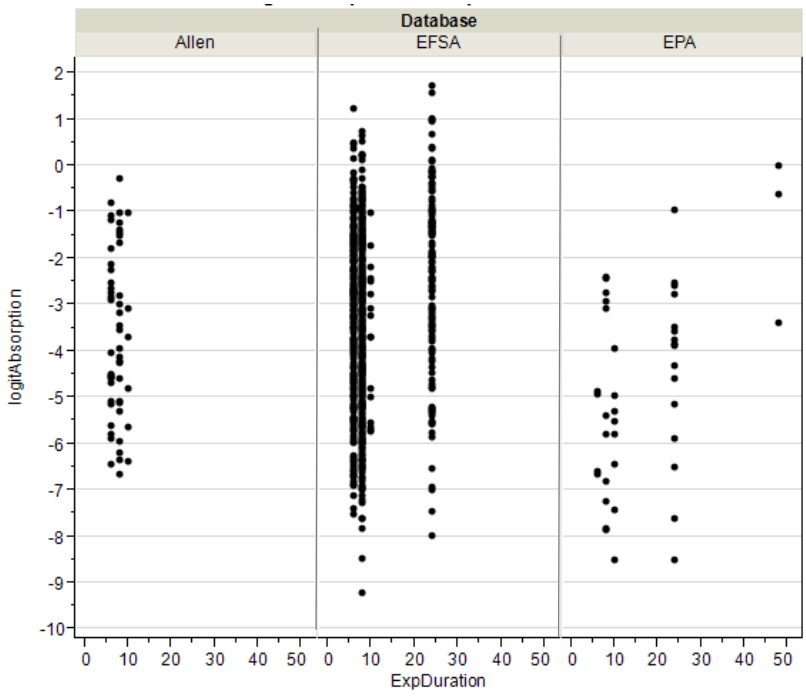
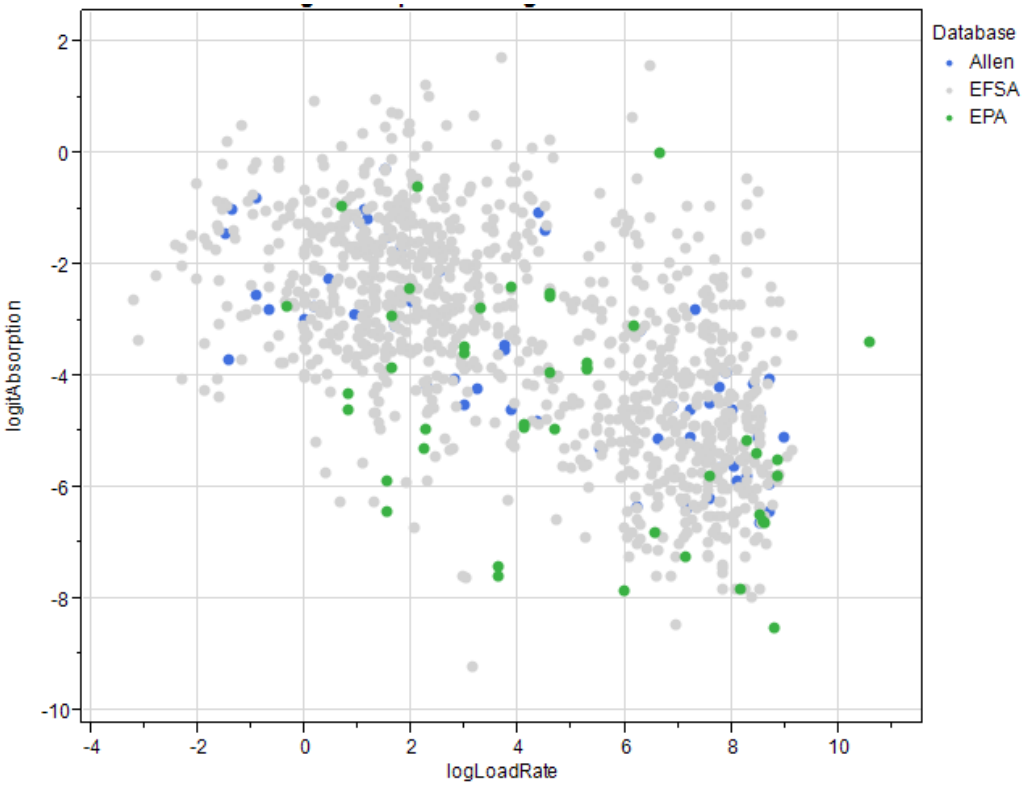
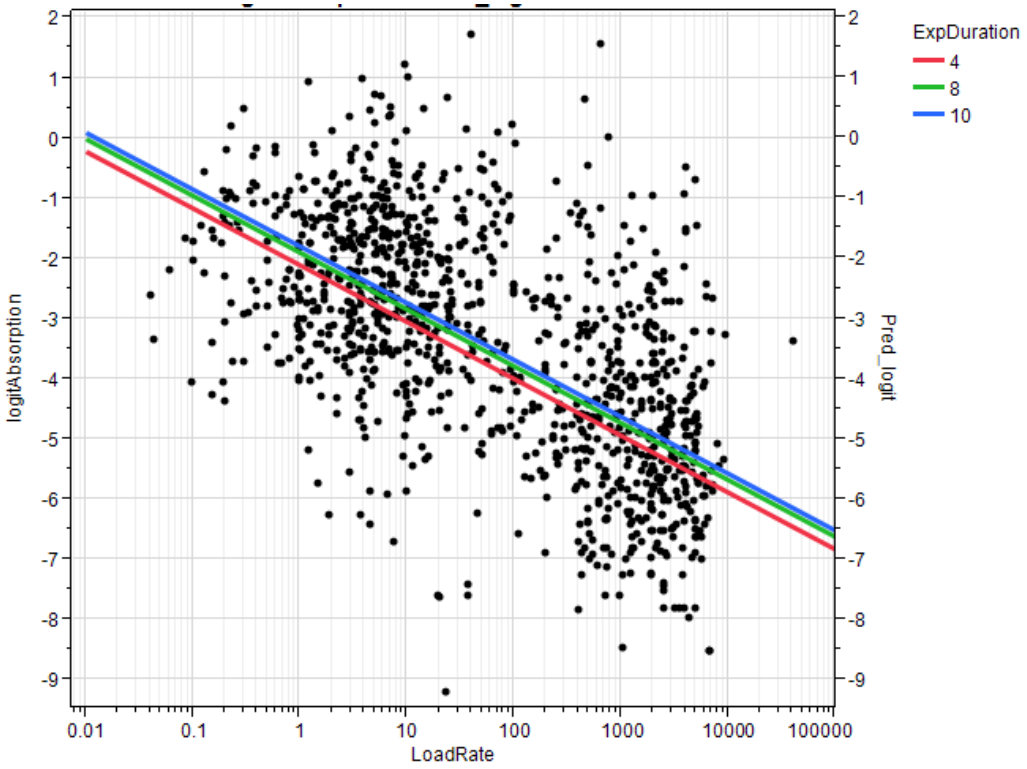


Figure 1411. Transformed Human in vitro Dermal Absorption Data Graphed in Relation to Dermal Loading



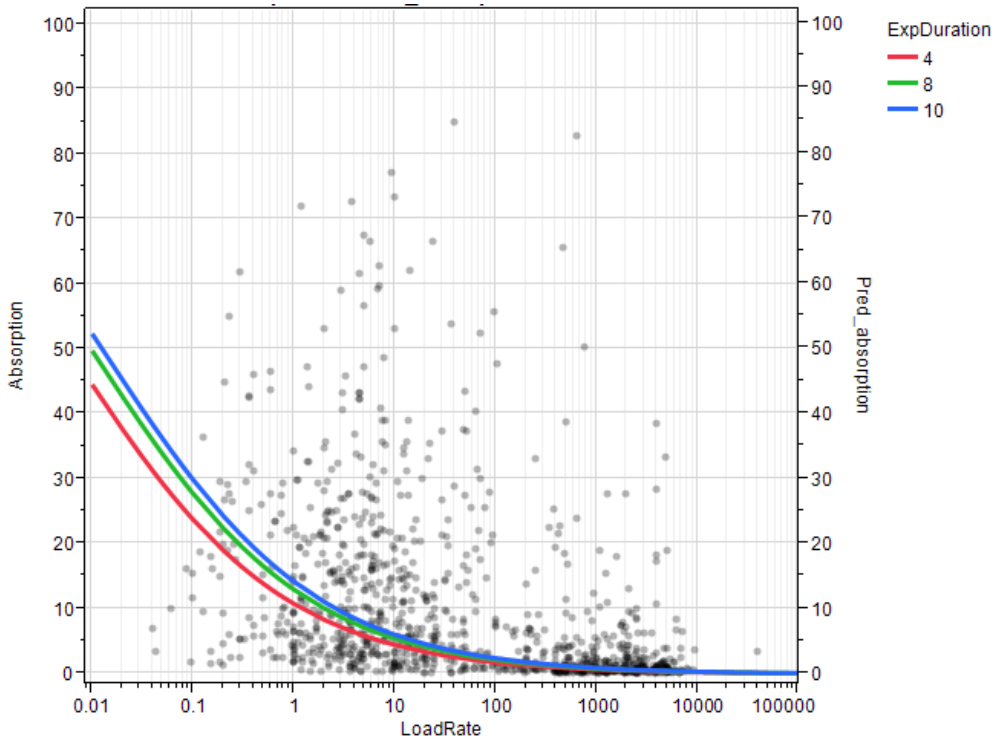
The logit transformation provides a clearer visual that percent dermal absorption appears to increase with longer exposure duration (Figure 13 above) and percent dermal absorption decreases with higher dermal loadings (Figure 14 above). A mixed-effects model analysis was performed and confirmed statistically significant trends for both exposure duration (positive association) and dermal loading (negative association). Figure 15 below shows the modeled logit absorption values at given exposure durations. The measured human *in vitro* absorption values are the black points, and the predicted values are shown by the colored lines, each corresponding to a given select exposure duration (4, 8 and 10 hours). More details, including additional analyses comparing human and rat dermal absorption values, as well as differences between *in vivo* and *in vitro* approaches, are provided in Appendix A.

Figure 1512. Model Predicted logit Dermal Absorption Values Across Exposure Durations



Conversion back from the logit transformation provides a more intuitive visual. Figure 16 below displays the prediction curves (in standard percentages) similarly overlayed on the measured human *in vitro* data (data points are greyed-out to enhance the visual). Modeled dermal absorption is shown for the same three select exposure durations shown in Figure 15 above (4, 8, and 10 hours).

Figure 1613. Model Predicted Dermal Absorption Values Across Exposure Durations



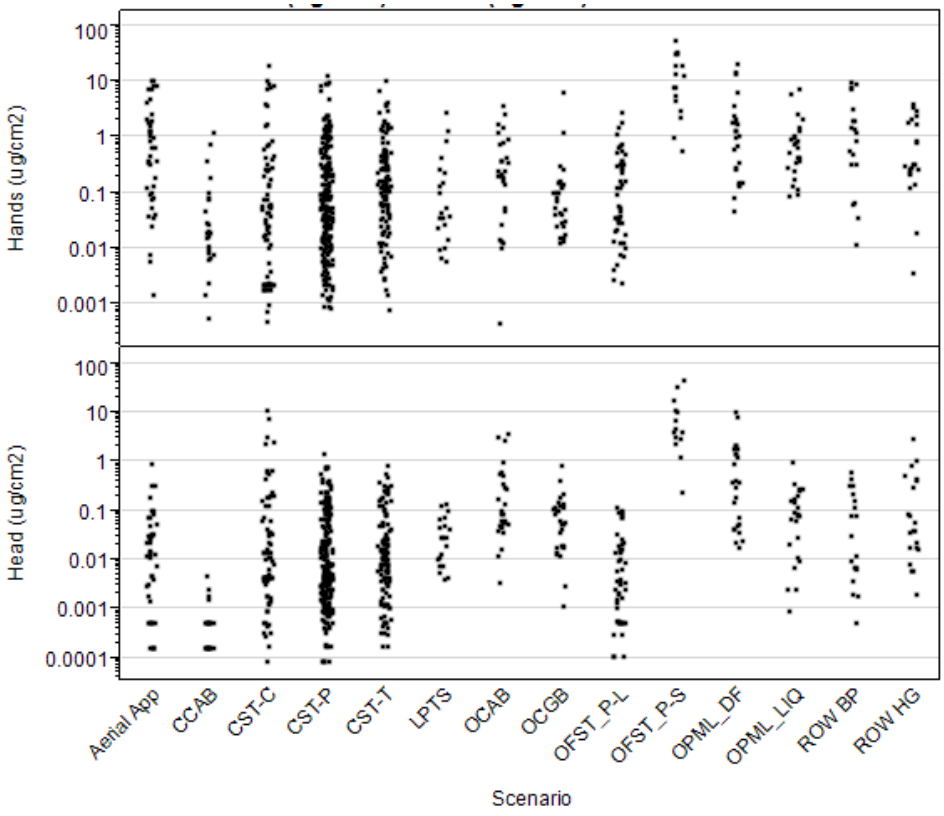
Statistical Analysis and Modeling Conclusions

Thus, from this modeling, exposure duration and dermal loading are important factors regarding the MEA. To the extent exposure monitoring studies are comprised of long exposure times prior to hand rinse or face/neck wipe sampling (e.g., 8 or 10 hours) and comprised of low dermal loading (e.g., 0.01 µg/cm^2), dermal absorption could be substantial, implying that the hand rinse and face/neck wipes may fail to accurately represent exposure as intended under relevant exposure monitoring study conditions.

While there are many studies where hand or head exposure was evaluated and measured at the end of the monitoring period (e.g., 8 hour or longer exposure time), most contemporary studies under consideration for the MEA sampled at two time points within the monitoring period, typically one about halfway through the monitoring and the second one at the end of the monitoring (total exposure being the sum of the samples). In those cases, the exposure time would be approximately 4 hours or less (assuming an 8-hour monitoring period). It follows that if the entire monitoring period in the study was low (e.g., 2 hours), the exposure time on the skin would therefore have been low. Additionally, to the extent there were 3 or more samples taken during the monitoring period, the exposure time on the skin (in between each sample) would be correspondingly lower. For example, in the data underlying EPA's Seed Treatment assessments, due to the natural breaks that workers take throughout the day, many participants had more than 2 hand wash samples, some had as many as 7 throughout their monitoring period. In those cases, the time available to "allow" for dermal absorption to take place would be very limited. For those reasons, the 4 hour exposure duration model is selected as the most appropriate frame of reference.

As previously mentioned, dermal loading is a more complicated variable to consider. With that in mind, Figure 6 is provided again below for reference, providing best estimates of expected dermal loading based on exposure monitoring studies, ranging from a low of about 0.01 µg/cm^2 to a high of about 10 µg/cm^2. Review of the modeling shown in Figure 16 – specifically the red line "4-hour model" - focusing on the low-end dermal loadings, absorption can be high over 4 hours, upwards of 50%, while for the upper-end dermal loading of 10 µg/cm^2, absorption is likely to be much lower over 4 hours, around 5%.

Figure 614. Observed Dermal Loadings of the Hands (µg/cm^2) and Head (µg/cm^2) Across Worker Scenarios



Aerial App = aerial applications; CCAB = closed-cab airblast; CST-C = commercial seed treatment, cleaning equipment; CST-P = commercial seed treatment, packaging seed; CST-T = commercial seed treatment, treating seed; LPTS = loading and planting treated seed; OCAB = open-cab airblast; OCGB = open-cab groundboom; OFST_P-L = on-farm seed treatment and planting, liquid formulations; OFST_P-S = on-farm seed treatment and planting, solid formulations; OPML_DF = open pour mixing and loading, dry flowables; OPML_LIQ = open pour mixing and loading, liquids; ROW BP = rights-of-way applications with backpack sprayer; ROW HG = rights-of-way applications with handgun sprayer

Importantly, the data in Figure 6 (repeated from previous) above are the *measured*, or observed, dermal loadings *after* sampling, not the dermal loading at the "start" of the exposure event. Based on the dermal absorption analysis and the red line "4-hour model" shown by the trend in Figure 16, observed dermal loadings, ranging from about 10 µg/cm^2 to 0.001 µg/cm^2, would have resulted from dermal absorption of about 5% to 60%, respectively. In other words, a range of *observed* dermal loadings of 10 µg/cm^2 to 0.001 µg/cm^2 could have "started" as dermal loadings ranging from about 10.5 µg/cm^2 to 0.003 µg/cm^2, or 1.05X to 3X higher than observed, respectively. These dermal-loading results based on modeling should be considered in the context of the 2X default factor currently used for the MEA.

In general, while the average dermal absorption across all studies was approximately 10% (see Table 4 above), this analysis showed that a higher absorption at lower dermal loadings typically seen in exposure monitoring studies is possible. This analysis also highlighted that while a high level of inefficiency is possible (e.g., failing to collect 50% or more of exposure residues), it may only occur at very low dermal loadings and high exposure durations. That is, at some dermal loadings, the 2X MEA adjustment may be considered appropriate while at other, higher dermal loadings, the MEA may be inapplicable and unnecessary.

All statistical analyses/modeling were conducted using SAS 9.4. All programs and SAS codes are attached and presented in the Appendix A.2.

5.2 Additional Considerations

While the analysis and modeling conducted point to the potential for conditions within exposure monitoring studies to be affected by dermal absorption, it is important to state or reiterate certain caveats.

- Hand rinse and face/neck wipe exposure monitoring techniques are likely more vigorous than the removal processes employed in laboratory dermal absorption studies. Consequently, it is possible that the hand rinse and face/neck wipe techniques in the exposure monitoring studies extract residue from the skin that, left alone, would have been absorbed.
- Human *in vivo* data is limited but there is evidence, as described in Allen, et al., 2021 and discussed in Appendix A, that *in vitro* studies (on which this analysis is based) may overestimate absorption in living organisms.
- Many exposure monitoring studies are either conducted during activities that are inherently of low exposure time or multiple hand rinse and face/neck wipe samples are administered throughout the day. In either case, the "residence time" on the skin (allowing for absorption to occur) is potentially much lower than the exposure durations considered in the modeling.
- There are uncertainties with dermal loading estimates. First, these estimates assume even/uniform distribution across the surface area of the hands and the face/neck. If exposure was, in reality, a consequence of more concentrated droplets such that the totals covered only, for example, 1% of the surface area, dermal loadings would be in the range of 1 µg/cm^2 to 1000 µg/cm^2, not 0.01 µg/cm^2 to 10 µg/cm^2. On the other hand, if these total daily samples occurred as a consequence of multiple "events" throughout the day, the dermal loading at each event would be even lower than estimated here. Ultimately, absent more detailed information on exposure characteristics, the estimates shown in Figure 16 are the best approximations available and reasonable for consideration of the MEA.
- Available dermal absorption data was conducted down to dermal loading levels of approximately 0.04 µg/cm^2, whereas, based on exposure monitoring studies and assumed skin distribution, in-field dermal loading results could be significantly lower. There is always uncertainty associated with extrapolating beyond the range of the data on which the model is based.

6.0 Path Forward

The application of the MEA by EPA was based on uncertainty raised in the peer review process related to the AHETF and their generation of pesticide handler exposure data. That bare skin sampling techniques such as hand rinses and face/neck wipes may be subject to missing potential exposure due to dermal absorption is not under dispute. Dermal absorption can begin immediately upon deposition onto the skin, and the sampling frequency required to completely mitigate this issue would be logistically impractical. The major question is whether the underestimation can be significant enough to warrant an adjustment. In lieu of appropriate supporting information and uncertainty based on published information, EPA has been implementing the MEA, conservatively assuming the hand rinse face/neck wipes are "missing" 50% of potential skin residues due to absorption, thereby doubling hand and head exposure values when those body parts contribute significantly (>20% on average) to total dermal exposure.

Following this current analysis, reviewing a wide array of dermal absorption data, it appears that under some conditions, dermal absorption can be high, for which any bare skin sampling techniques would consequently fail to capture the complete exposure potential they intend to represent. With this more detailed and thorough consideration, there are various potential options for the MEA policy. For each option the MEA would continue to apply to studies where contribution of hand and head exposure to total dermal exposure is greater than 20%.[26] The options considered are as follows:

1. No change to the MEA – continue to increase hand and head exposures by 2X (assuming 50% inefficiency) and proceed with adjustments to all existing data (i.e., apply to those datasets where MEA has yet to be applied).
2. Remove the MEA from all data.
3. Change the MEA from a 2X adjustment (assuming 50% inefficiency) to a higher or lower single default value.
4. Instead of a single default MEA value, adjust by each monitored individual in each study using a generic dermal absorption model (like that presented in this review), based on dermal skin loading and exposure time for the monitored individual.
5. Instead of a single default MEA value, adjust by each monitored individual using chemical-specific dermal absorption data (by chemical, dermal skin loading and exposure time).

While our analysis in this paper demonstrates that in some cases dermal absorption can be substantial, only in some conditions is dermal absorption upwards of 50% or higher, and those conditions are not considered representative of the exposure monitoring studies in question. Therefore, EPA believes the MEA can be refined for future use. That eliminates Options 1 and 2 above. The analysis that was conducted has shown the sensitivity of dermal absorption to various factors (dermal loading, exposure duration, chemical, etc.), which provides support for a chemical-specific approach (Option 5). However, as a practical matter and from a large-scale generic database perspective, either applying a single default MEA value across all monitored individuals in applicable studies or applying a dermal-loading based model are both reasonable, resource-appropriate, and efficient computational approaches. Either option 3 or 4 is therefore preferred over Option 5. While slightly more resource-intensive,

[26] This percentage is proposed based on pragmatic considerations rather than any quantitative analysis. In cases where the contribution of hands and head are less than 20%, application of the described modeling will, similar to the previous MEA approach, have minimal impact on the overall dermal exposure estimate.

Option 4 is preferred over Option 3 as it is a more refined approach and also computationally reasonable.

Recommendations:
Option 4 will be applied by focusing on the modeling results for low dermal loadings (e.g., 0.01 to 10 µg/cm^2) at 4 hours exposure time, as well as the considerations outlined in Section 5.2 above, where average dermal contribution, of hands and head, is higher than 20%. EPA would adjust each monitored worker's hand and head exposure based on the observed dermal loading estimate (µg/cm^2) and its corresponding potential absorption from the modeling discussed in this analysis. For example, instead of the one-size-fits-all 2X adjustment currently applied, using the model in Figure 16 above, a hand exposure measurement estimated to be 10 µg/cm^2 would be adjusted by a factor of 1.1X (corresponding to approximately 7% dermal absorption), while a measurement of 0.01 µg/cm^2 would be adjusted by a factor of 2.3X (corresponding to approximately 56% absorption)[27].

Datasets currently using MEA will be revised to reflect this dermal-loading based adjustment – instead of the one-size-fits-all 2X adjustment - and MEA will now be considered for datasets where it has not yet been applied. Despite this approach, case-specific suggestions and rationales for monitoring studies where dermal absorption is claimed to be of less concern can continue to be made for further refinement. Furthermore, this analysis was based on dermal absorption laboratory studies. This paper previously described how these laboratory dermal absorption studies are being used at this time because they are currently the best available analog for monitoring study residue removal techniques. Direct method validation of the efficiency of the hand rinse and face/neck wipe techniques used in exposure monitoring studies also remains an option for reconsidering the MEA.

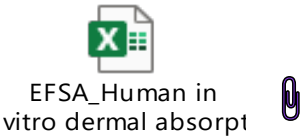
[27] Estimated adjustment factors based on modeling presented in Figure 16. Model Predicted Dermal Absorption Values Across Exposure Durations

APPENDIX A Statistical Analysis and Modeling

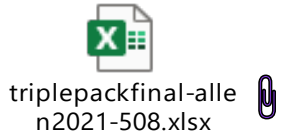
Appendix A.1 Data Files

EPA Internal Database: AppA_OPP_MEA_Response_010821.xlsx

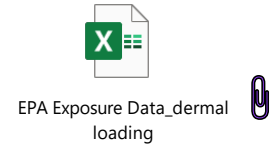
EFSA, 2017: Human in vitro dermal absorption PPPs dataset.xlsx



Allen, et al., 2021: triplepackfinal-allen2021-508.xlsx



Dermal Dose/Loading Estimates: EPA Exposure Data_dermal loading estimates.xlsx



Appendix A.2 Statistical Data Analysis

A.2.1 Conclusions

- Loading rate significantly and negatively associated with the percent absorption of *in vitro* data, (p-value < 0.001).

- The percent absorption was significantly different between *in vitro* and *in vivo* data (p-values < 0.001). However, this difference should be interpreted cautiously due to the small sample size of *in vivo* data and the lack of data at low loading rates.

- Exposure duration significantly and positively associated with the percent absorption (p-value < 0.001).

Below is the statistical equation of mean absorption (%) without random error terms of the data analysis using only human data:

% absorption = 100 × exp(A)/{1 + exp(A)},

where A = – 2.3218 – 1.4893 × (0 if Study Type= *in vitro*, 1 if Study Type= *in vivo*)
– 0.4103 × log(loading rate, $\mu g/cm^2$)
+ 0.3094 × log(loading rate $\mu g/cm^2$) × (0 if Study Type = *in vitro*, 1 if Study Type = *in vivo*)
+ 0.05221 × exposure duration *hours*

Based on the initial analysis that included both human and rat data, the percent absorption of rat was significantly higher than human (p-value < 0.001).

A.2.2 Databases

There were three databases considered for use to evaluate the percent dermal absorption.

The EFSA database included only human *in vitro* studies. After cleaning (using the average of replicates, replacing absorption = 0.01% for one datapoint with absorption = 0; deleting a few records with negative or missing absorption and missing loading rate), there was a total of 1037 datapoints.

The EPA database included both *in vitro* and *in vivo* studies of multiple species (human, rat, monkey, mouse, porcine, and rabbit). Due to the small sample size of monkey, mouse, porcine, and rabbit, only rat and human data were included in the analyses. After cleaning (replacing absorption = 0.01% for a few datapoints with absorption = 0; deleting records with missing absorption, loading rate, wash time (i.e., exposure duration), and/or information of in vitro/in vivo), there was a total of 569 datapoints from rat and human studies (44 human – *in vitro*, 57 human – *in vivo*, 38 rat – *in vitro*, and 430 rat – *in vivo*).

The database from Allen et. al 2021 publication included human and rat *in vitro* and *in vivo* studies. After cleaning (including only the data of the 24-hour skin sample collection), there was a total of 168 datapoints (56 human – *in vitro*, 56 rat – *in vitro*, and 56 rat – *in vivo*).

Table A.2.2.T1: Numbers of datapoints and chemicals in the combined dataset used for data analyses

Counts	Database	HUMAN		RAT		*Total*
		In Vitro	*In Vivo*	*In Vitro*	*In Vivo*	
Datapoints	**Allen**	56		56	116	*228*
	EFSA	1037				*1037*
	EPA	44	57	38	430	*569*
	Total	*1137*	*57*	*94*	*546*	*1834*
Chemicals	***Total***	*225*	*15*	*38*	*54*	*251*

Table A.2.2.T2: Ranges of percent absorption, loading rate, and exposure duration in the analysis dataset

Species	StudyType	NN	Variable	Minimum	Maximum
HUMAN	InVitro	1137	Absorption (%) Loading Rate (ug/cm2) Exposure Duration (hrs)	0.01 0.04 6.00	84.84 40200.00 48.00
	InVivo	57	Absorption (%) Loading Rate (ug/cm2) Exposure Duration (hrs)	0.22 1.47 0.25	73.90 4160.00 24.00
RAT	InVitro	94	Absorption (%) Loading Rate (ug/cm2) Exposure Duration (hrs)	0.04 0.24 6.00	74.05 40100.00 48.00
	InVivo	546	Absorption (%) Loading Rate (ug/cm2) Exposure Duration (hrs)	0.01 0.25 0.50	61.13 8000.00 144.00

Below, Figures A.2.5.F5 to A.2.5.F8 present the scatterplots of absorption data vs. exposure duration. Figures A.2.5.F9 to A.2.5.F12 present the scatterplots of absorption data vs. loading rate.

A.2.3 Statistical methods

Logit transformation was applied to percent absorption data to achieve normality assumption. Loading rate were substantially left skew; hence, natural log-transformation was applied to loading rate. Mixed-effects models were used to evaluate the associations between percent of dermal absorption vs. loading rate and exposure duration. Chemical was set as experimental subject. An unstructured variance-covariance matrix with random intercept, random effect log(loading rate), and random exposure duration was selected for use in the final models of all analyses since the AIC (Akaike information criterion) values were smaller than other simpler models with either random intercept only, random intercept and random log(loading rate, or random intercept and random exposure duration.

Initial analyses

Analyses using EPA database– a model without species or study type
This simple analysis used only the EPA database and assumed that there were no effects of species or study type on the absorption; hence, only log(loading rate) and exposure duration were included as fixed effects in the model.

Analysis using EPA database – a model also including species and study type
This analysis used only the EPA database. The full model included species (human *vs.* rat), study type (*in vivo* vs. *in vitro*), exposure duration, log(loading rate), and all 2-way interactions between the factors as fixed effects. Likelihood ratio tests were used to select the fixed effects for the final model.

Analysis using the combined database – both human and rat data
The full model of this analysis included species (human *vs.* rat), study type (*in vivo* vs. *in vitro*), exposure duration, log(loading rate), and all 2-way interactions between the factors as fixed effects. Likelihood ratio tests were used to select the fixed effects for the final model.

Main analysis using combined database – only human data
From the initial analyses, there was evidence that the percent absorption was different between rat and human; therefore, the main analysis using the combined database only included the human data.

The full model included exposure duration, log(loading rate), study type (in vivo vs. in vitro), and all 2-way interactions between the factors as fixed effects in the model. Likelihood ratio tests were used to select the fixed effects for the final model.

A.2.4 Results of Data Analysis using combined database - only human data

This main data analysis included only human data of the combined database. Based on likelihood ratio tests, the final model included exposure duration, log(loading rate), study type (*in vivo* vs. *in vitro*), and study type × log(loading rate) interaction as fixed effects. Table A.2.4.T3 presents the estimated coefficients of the fixed effects in the final model.

For *in vitro*, loading rate significantly and negatively associated with the percent absorption (p-value < 0.001).

The percent absorption was significantly different between *in vitro* and *in vivo* data (p-values < 0.001). However, this difference should be interpreted cautiously due to the small sample size of *in vivo* data (Table A.2.2.T1) and the lack of data at low range and high range loading rates (Table A.2.2.T2 and Figures A.2.4.F3 and A.2.4.F4).

Exposure duration significantly and positively associated with the percent absorption (p-value < 0.001).

Below is the statistical equation of mean absorption (%) without random error terms of the data analysis using only human data (re-written from Table A.2.4.T3):

% absorption = 100 × exp(A)/{1 + exp(A)},

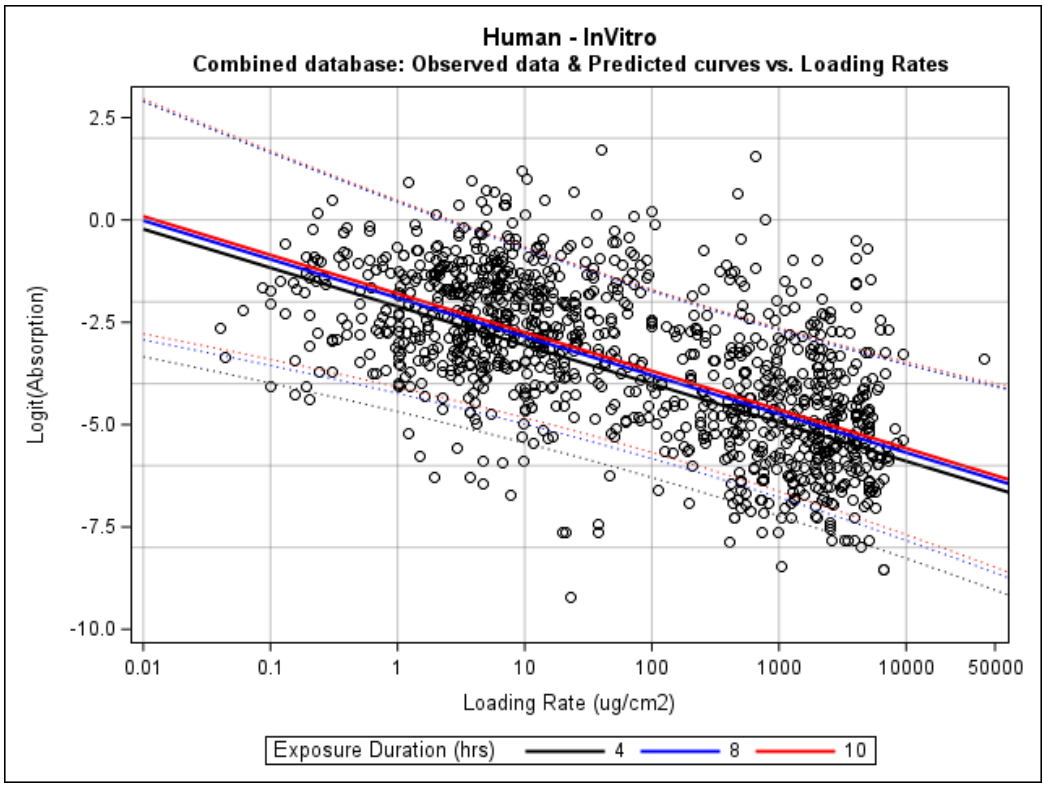
where A = – 2.3218 – 1.4893 × (0 if Study Type = *in vitro*, 1 if Study Type = *in vivo*)
– 0.4103 × log(loading rate, $\mu g/cm^2$)
+ 0.3094 × log(loading rate $\mu g/cm^2$) × (0 if Study Type = *in vitro*, 1 if Study Type = *in vivo*)
+ 0.05221 × exposure duration *hours*

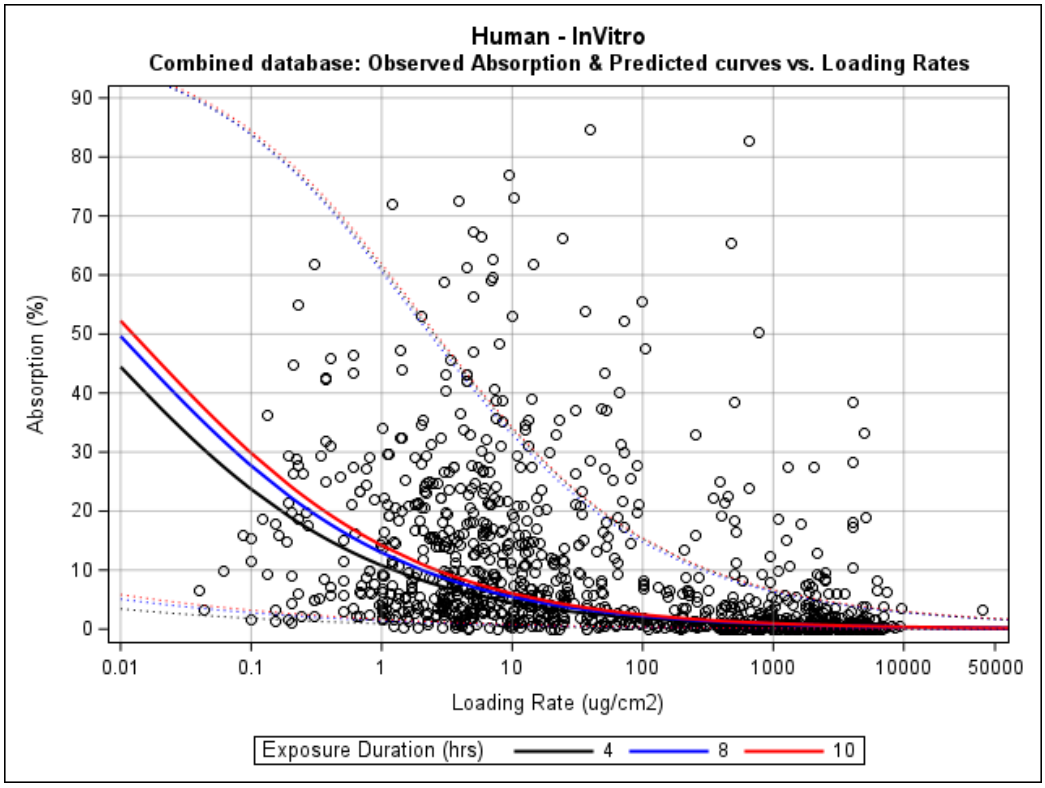
Table A.2.4.T4 and Figures A.2.4.F1- A.2.4.F4 present the estimated mean of percent absorption of all chemicals.

Table A.2.4.T3: Estimated coefficients of fixed effects in the final model using only human data of combined database

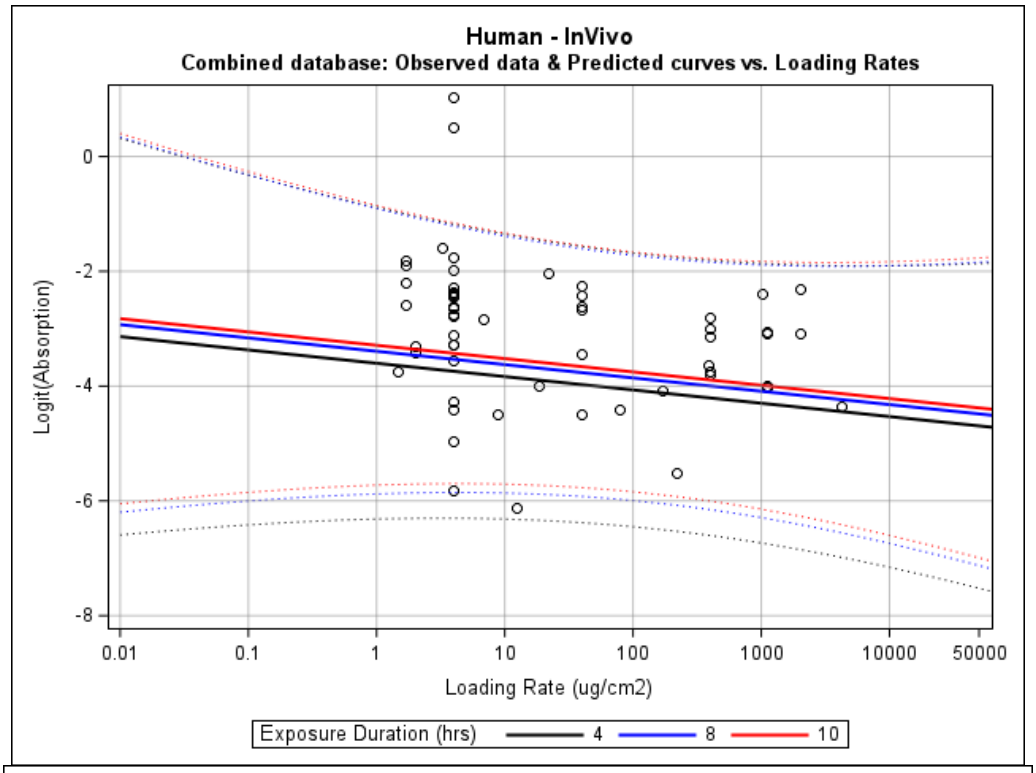
Solution for Fixed Effects									
Effect	**StudyType**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
Intercept		-2.3218	0.1534	236	-15.14	<.0001	0.05	-2.6240	-2.0197
StudyType	InVivo	-1.4893	0.4527	684	-3.29	0.0011	0.05	-2.3781	-0.6005
StudyType	InVitro	0	.	.	.	.	.	.	.
LogLoadRate		-0.4103	0.01337	218	-30.68	<.0001	0.05	-0.4366	-0.3839
ExpDuration		0.05221	0.01257	51	4.15	0.0001	0.05	0.02697	0.07746
LogLoadRate*StudyType	InVivo	0.3094	0.08528	684	3.63	0.0003	0.05	0.1420	0.4769
LogLoadRate*StudyType	InVitro	0	.	.	.	.	.	.	.

Figures A.2.4.F1- A.2.4.F2: All observed human – *in vitro* data and estimated mean curves using combined database





Figures A.2.4.F3- A.2.4.F4: All observed human – *in vivo* data and estimated mean curves using combined database



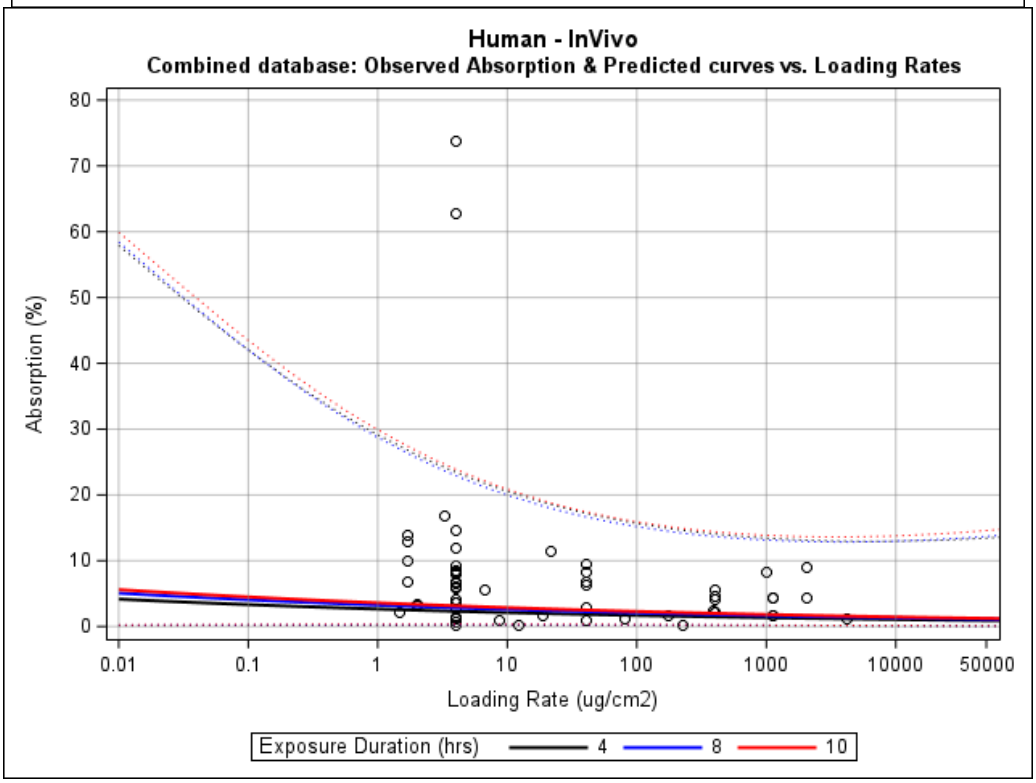


Table A.2.4.T4: Estimated mean absorption values for human using combined database

Estimated mean absorption values for human					
Exposure Duration (hrs)	**Loading Rate (µg/cm²)**	***In vitro***		***In vivo***	
		Est. Mean (%)	**95% CI**	**Est. Mean (%)**	**95% CI**
4	0.01	44.43	(3.42, 94.75)	4.16	(0.14, 57.88)
4	0.02	37.57	(2.84, 92.52)	3.89	(0.14, 52.97)
4	0.03	33.75	(2.55, 90.84)	3.74	(0.15, 50.13)
4	0.04	31.17	(2.36, 89.47)	3.63	(0.15, 48.14)
4	0.05	29.24	(2.22, 88.28)	3.56	(0.16, 46.61)
4	0.06	27.71	(2.11, 87.23)	3.49	(0.16, 45.38)
4	0.07	26.46	(2.02, 86.29)	3.44	(0.16, 44.35)
4	0.08	25.41	(1.94, 85.42)	3.40	(0.16, 43.47)
4	0.09	24.51	(1.88, 84.63)	3.36	(0.16, 42.7)
4	0.10	23.72	(1.82, 83.88)	3.32	(0.16, 42.02)
4	0.20	18.96	(1.49, 78.32)	3.11	(0.17, 37.72)
4	0.30	16.53	(1.32, 74.52)	2.99	(0.17, 35.36)
4	0.40	14.97	(1.21, 71.59)	2.90	(0.18, 33.77)
4	0.50	13.84	(1.14, 69.2)	2.84	(0.18, 32.58)
4	0.60	12.97	(1.07, 67.17)	2.79	(0.18, 31.64)
4	0.70	12.27	(1.02, 65.41)	2.75	(0.18, 30.86)
4	0.80	11.70	(0.98, 63.86)	2.71	(0.18, 30.2)
4	0.90	11.21	(0.95, 62.47)	2.68	(0.18, 29.64)
4	1.00	10.78	(0.92, 61.22)	2.65	(0.18, 29.14)
4	2.00	8.34	(0.74, 52.74)	2.48	(0.18, 26.11)
4	3.00	7.15	(0.65, 47.75)	2.38	(0.18, 24.52)
4	4.00	6.41	(0.59, 44.26)	2.32	(0.18, 23.47)
4	5.00	5.88	(0.54, 41.61)	2.27	(0.18, 22.7)
4	6.00	5.48	(0.51, 39.5)	2.22	(0.18, 22.1)
4	7.00	5.16	(0.49, 37.75)	2.19	(0.18, 21.61)
4	8.00	4.90	(0.46, 36.27)	2.16	(0.18, 21.21)
4	9.00	4.68	(0.45, 34.98)	2.14	(0.18, 20.86)
4	10.00	4.49	(0.43, 33.86)	2.12	(0.18, 20.55)
4	20.00	3.42	(0.34, 27.03)	1.98	(0.18, 18.74)
4	30.00	2.91	(0.29, 23.53)	1.90	(0.17, 17.83)
4	40.00	2.59	(0.26, 21.28)	1.84	(0.17, 17.24)
4	50.00	2.37	(0.24, 19.65)	1.80	(0.17, 16.82)

Estimated mean absorption values for human					
Exposure Duration (hrs)	Loading Rate (µg/cm²)	*In vitro*		*In vivo*	
		Est. Mean (%)	95% CI	Est. Mean (%)	95% CI
4	60.00	2.20	(0.22, 18.41)	1.77	(0.16, 16.49)
4	70.00	2.07	(0.21, 17.41)	1.75	(0.16, 16.23)
4	80.00	1.96	(0.2, 16.58)	1.72	(0.16, 16.02)
4	90.00	1.87	(0.19, 15.89)	1.70	(0.16, 15.83)
4	100.00	1.79	(0.18, 15.28)	1.68	(0.16, 15.67)
4	200.00	1.36	(0.14, 11.83)	1.57	(0.15, 14.77)
4	300.00	1.15	(0.12, 10.18)	1.51	(0.14, 14.33)
4	400.00	1.02	(0.11, 9.15)	1.47	(0.14, 14.07)
4	500.00	0.94	(0.1, 8.43)	1.44	(0.13, 13.88)
4	600.00	0.87	(0.09, 7.88)	1.41	(0.13, 13.75)
4	700.00	0.82	(0.08, 7.44)	1.39	(0.13, 13.64)
4	800.00	0.77	(0.08, 7.08)	1.37	(0.12, 13.55)
4	900.00	0.74	(0.08, 6.79)	1.35	(0.12, 13.48)
4	1000.00	0.71	(0.07, 6.53)	1.34	(0.12, 13.43)
8	0.01	49.63	(5.07, 94.78)	5.07	(0.2, 58.41)
8	0.02	42.58	(4.25, 92.52)	4.75	(0.22, 53.36)
8	0.03	38.57	(3.83, 90.82)	4.57	(0.22, 50.43)
8	0.04	35.81	(3.55, 89.42)	4.44	(0.23, 48.37)
8	0.05	33.74	(3.35, 88.22)	4.35	(0.23, 46.79)
8	0.06	32.08	(3.19, 87.15)	4.27	(0.24, 45.52)
8	0.07	30.72	(3.06, 86.18)	4.21	(0.24, 44.46)
8	0.08	29.57	(2.95, 85.3)	4.15	(0.24, 43.55)
8	0.09	28.57	(2.85, 84.49)	4.11	(0.24, 42.75)
8	0.10	27.70	(2.77, 83.73)	4.06	(0.25, 42.05)
8	0.20	22.38	(2.29, 78.04)	3.80	(0.26, 37.6)
8	0.30	19.62	(2.04, 74.14)	3.65	(0.26, 35.16)
8	0.40	17.83	(1.87, 71.15)	3.55	(0.27, 33.51)
8	0.50	16.52	(1.75, 68.7)	3.48	(0.27, 32.28)
8	0.60	15.52	(1.66, 66.63)	3.42	(0.27, 31.31)
8	0.70	14.71	(1.59, 64.83)	3.37	(0.28, 30.51)
8	0.80	14.03	(1.52, 63.25)	3.32	(0.28, 29.83)
8	0.90	13.46	(1.47, 61.83)	3.28	(0.28, 29.25)
8	1.00	12.96	(1.42, 60.55)	3.25	(0.28, 28.74)
8	2.00	10.08	(1.15, 51.93)	3.04	(0.28, 25.62)

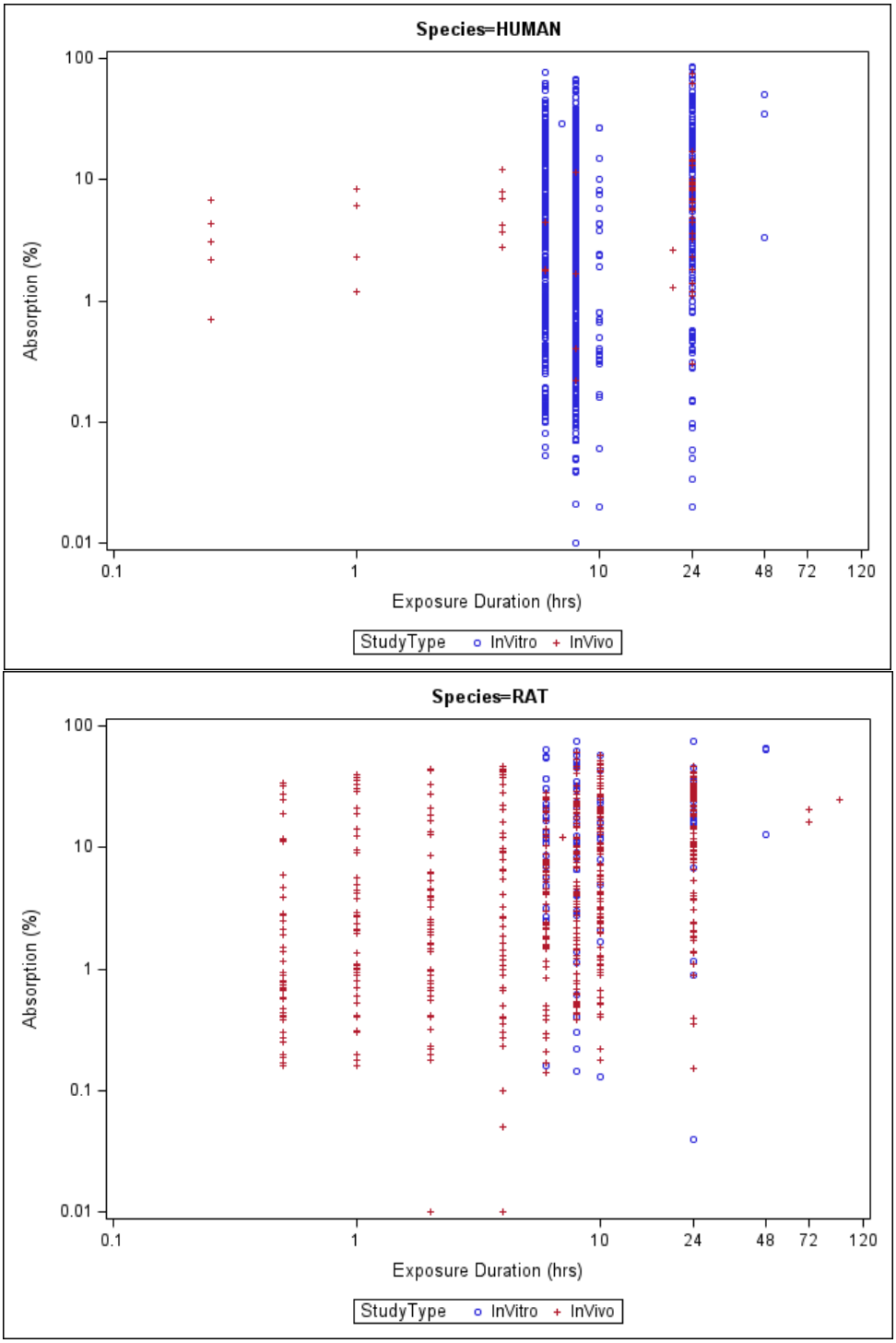
Estimated mean absorption values for human					
Exposure Duration (hrs)	Loading Rate (µg/cm²)	*In vitro*		*In vivo*	
		Est. Mean (%)	95% CI	Est. Mean (%)	95% CI
8	3.00	8.67	(1.01, 46.88)	2.92	(0.29, 24)
8	4.00	7.78	(0.92, 43.37)	2.84	(0.29, 22.93)
8	5.00	7.15	(0.86, 40.71)	2.78	(0.29, 22.15)
8	6.00	6.67	(0.81, 38.59)	2.73	(0.29, 21.54)
8	7.00	6.28	(0.76, 36.84)	2.69	(0.29, 21.05)
8	8.00	5.97	(0.73, 35.36)	2.65	(0.28, 20.64)
8	9.00	5.70	(0.7, 34.08)	2.62	(0.28, 20.28)
8	10.00	5.47	(0.68, 32.96)	2.59	(0.28, 19.98)
8	20.00	4.18	(0.53, 26.2)	2.42	(0.28, 18.17)
8	30.00	3.56	(0.46, 22.76)	2.33	(0.27, 17.27)
8	40.00	3.18	(0.41, 20.55)	2.26	(0.27, 16.69)
8	50.00	2.91	(0.38, 18.96)	2.21	(0.26, 16.27)
8	60.00	2.70	(0.36, 17.75)	2.17	(0.26, 15.96)
8	70.00	2.54	(0.34, 16.78)	2.14	(0.26, 15.71)
8	80.00	2.41	(0.32, 15.98)	2.11	(0.25, 15.5)
8	90.00	2.30	(0.31, 15.3)	2.09	(0.25, 15.32)
8	100.00	2.20	(0.29, 14.72)	2.07	(0.25, 15.17)
8	200.00	1.67	(0.22, 11.39)	1.93	(0.23, 14.32)
8	300.00	1.41	(0.19, 9.8)	1.85	(0.22, 13.92)
8	400.00	1.26	(0.17, 8.81)	1.80	(0.21, 13.68)
8	500.00	1.15	(0.15, 8.12)	1.76	(0.21, 13.52)
8	600.00	1.07	(0.14, 7.59)	1.73	(0.2, 13.4)
8	700.00	1.00	(0.13, 7.18)	1.71	(0.2, 13.31)
8	800.00	0.95	(0.13, 6.84)	1.68	(0.19, 13.24)
8	900.00	0.91	(0.12, 6.55)	1.66	(0.19, 13.19)
8	1000.00	0.87	(0.11, 6.31)	1.65	(0.18, 13.14)
10	0.01	52.24	(5.84, 95.07)	5.60	(0.23, 59.91)
10	0.02	45.15	(4.91, 92.92)	5.24	(0.25, 54.88)
10	0.03	41.07	(4.42, 91.3)	5.04	(0.26, 51.94)
10	0.04	38.25	(4.1, 89.96)	4.91	(0.27, 49.88)
10	0.05	36.11	(3.87, 88.81)	4.80	(0.27, 48.29)
10	0.06	34.40	(3.69, 87.78)	4.72	(0.28, 47)
10	0.07	32.99	(3.54, 86.86)	4.65	(0.28, 45.93)
10	0.08	31.79	(3.41, 86.01)	4.59	(0.28, 45.01)

Estimated mean absorption values for human					
Exposure Duration (hrs)	Loading Rate (µg/cm²)	*In vitro*		*In vivo*	
		Est. Mean (%)	95% CI	Est. Mean (%)	95% CI
10	0.09	30.75	(3.31, 85.23)	4.54	(0.28, 44.2)
10	0.10	29.84	(3.21, 84.5)	4.49	(0.29, 43.49)
10	0.20	24.24	(2.65, 78.99)	4.20	(0.3, 38.96)
10	0.30	21.32	(2.36, 75.21)	4.04	(0.31, 36.47)
10	0.40	19.41	(2.17, 72.29)	3.93	(0.31, 34.79)
10	0.50	18.02	(2.04, 69.89)	3.85	(0.32, 33.53)
10	0.60	16.94	(1.93, 67.86)	3.78	(0.32, 32.53)
10	0.70	16.07	(1.84, 66.1)	3.72	(0.32, 31.71)
10	0.80	15.34	(1.77, 64.54)	3.67	(0.32, 31.02)
10	0.90	14.72	(1.71, 63.14)	3.63	(0.32, 30.42)
10	1.00	14.19	(1.66, 61.87)	3.59	(0.33, 29.89)
10	2.00	11.07	(1.34, 53.31)	3.36	(0.33, 26.69)
10	3.00	9.53	(1.18, 48.25)	3.23	(0.33, 25.01)
10	4.00	8.56	(1.07, 44.72)	3.14	(0.33, 23.91)
10	5.00	7.87	(1, 42.04)	3.07	(0.33, 23.1)
10	6.00	7.35	(0.94, 39.9)	3.02	(0.33, 22.47)
10	7.00	6.93	(0.89, 38.12)	2.97	(0.33, 21.97)
10	8.00	6.58	(0.85, 36.62)	2.93	(0.33, 21.54)
10	9.00	6.29	(0.82, 35.32)	2.90	(0.33, 21.18)
10	10.00	6.04	(0.79, 34.18)	2.87	(0.33, 20.86)
10	20.00	4.61	(0.62, 27.28)	2.68	(0.32, 18.99)
10	30.00	3.94	(0.54, 23.74)	2.58	(0.32, 18.06)
10	40.00	3.51	(0.48, 21.47)	2.51	(0.31, 17.46)
10	50.00	3.21	(0.44, 19.83)	2.45	(0.31, 17.04)
10	60.00	2.99	(0.41, 18.58)	2.41	(0.3, 16.71)
10	70.00	2.81	(0.39, 17.57)	2.37	(0.3, 16.46)
10	80.00	2.67	(0.37, 16.74)	2.34	(0.3, 16.24)
10	90.00	2.54	(0.36, 16.04)	2.31	(0.29, 16.06)
10	100.00	2.44	(0.34, 15.44)	2.29	(0.29, 15.91)
10	200.00	1.85	(0.26, 11.98)	2.14	(0.27, 15.04)
10	300.00	1.57	(0.22, 10.32)	2.05	(0.26, 14.63)
10	400.00	1.40	(0.2, 9.29)	2.00	(0.25, 14.4)
10	500.00	1.28	(0.18, 8.57)	1.95	(0.24, 14.23)
10	600.00	1.18	(0.16, 8.02)	1.92	(0.23, 14.12)

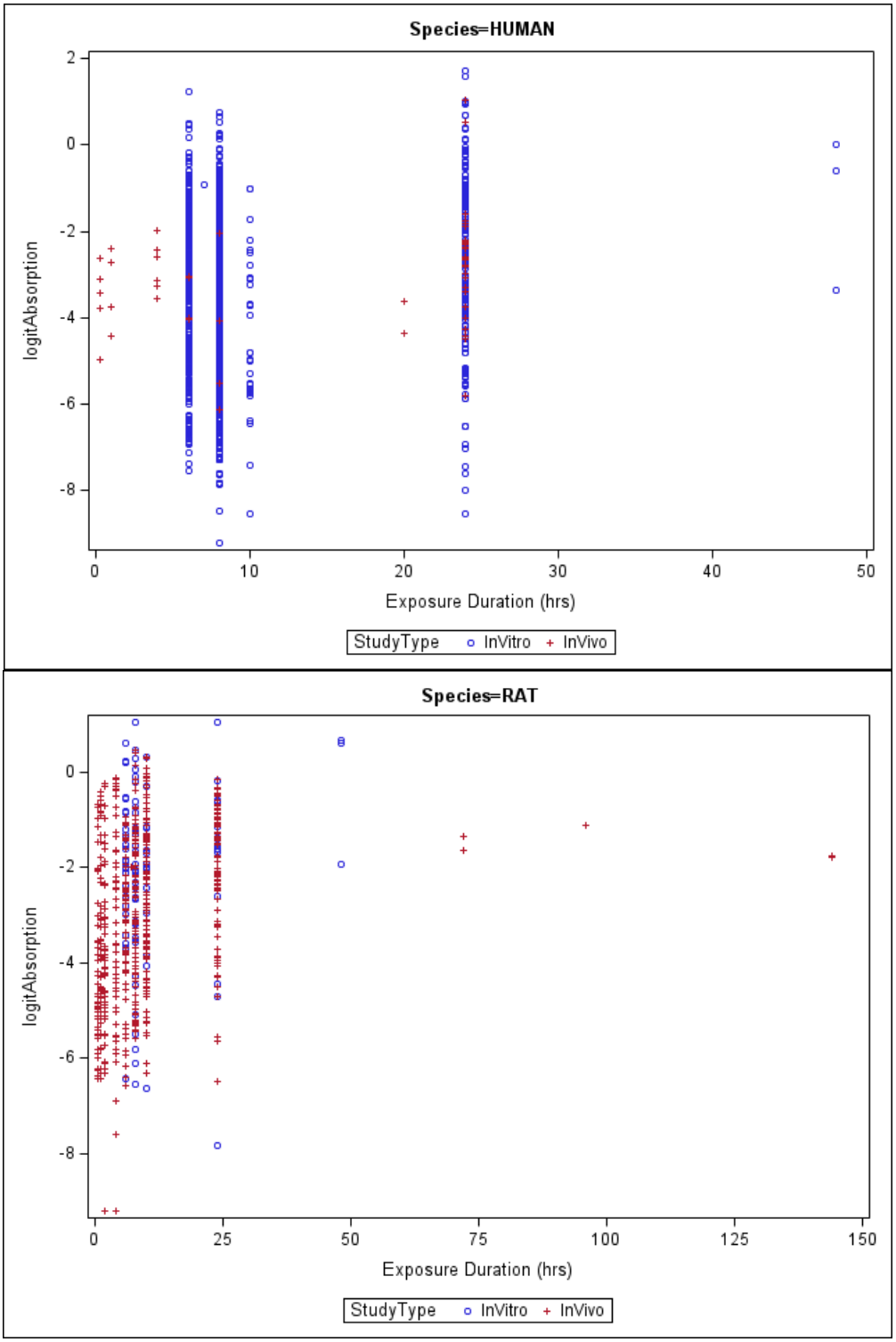
Estimated mean absorption values for human					
Exposure Duration (hrs)	**Loading Rate (µg/cm²)**	***In vitro***		***In vivo***	
		Est. Mean (%)	**95% CI**	**Est. Mean (%)**	**95% CI**
10	700.00	1.11	(0.15, 7.59)	1.89	(0.23, 14.03)
10	800.00	1.05	(0.15, 7.23)	1.87	(0.22, 13.96)
10	900.00	1.00	(0.14, 6.93)	1.84	(0.22, 13.9)
10	1000.00	0.96	(0.13, 6.67)	1.82	(0.21, 13.86)

A.2.5 Scatterplots of percent absorption data vs. exposure duration or loading rate

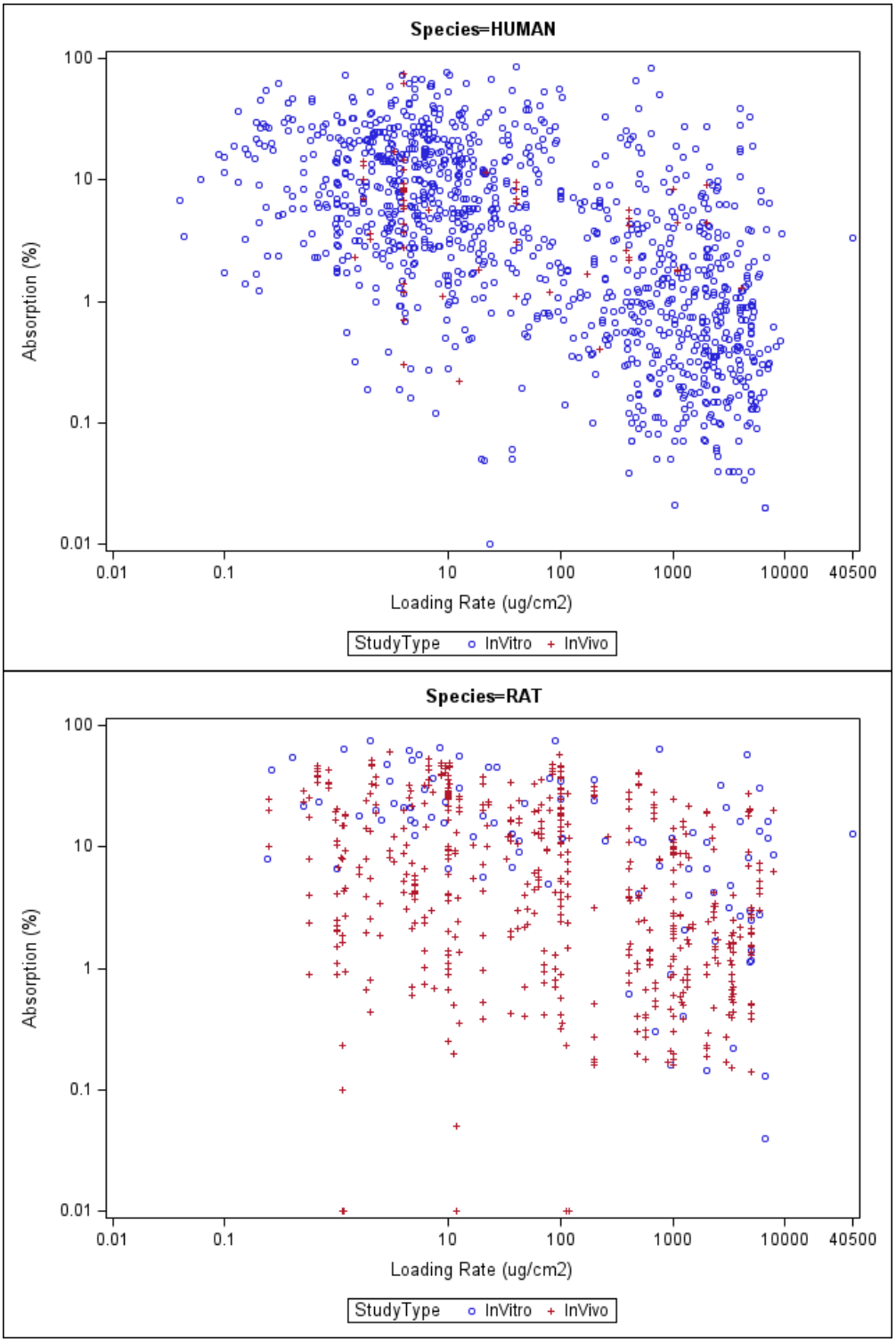
Figures A.2.5.F5- A.2.5.F6: scatterplots of percent absorption vs. exposure duration by study type using combined database



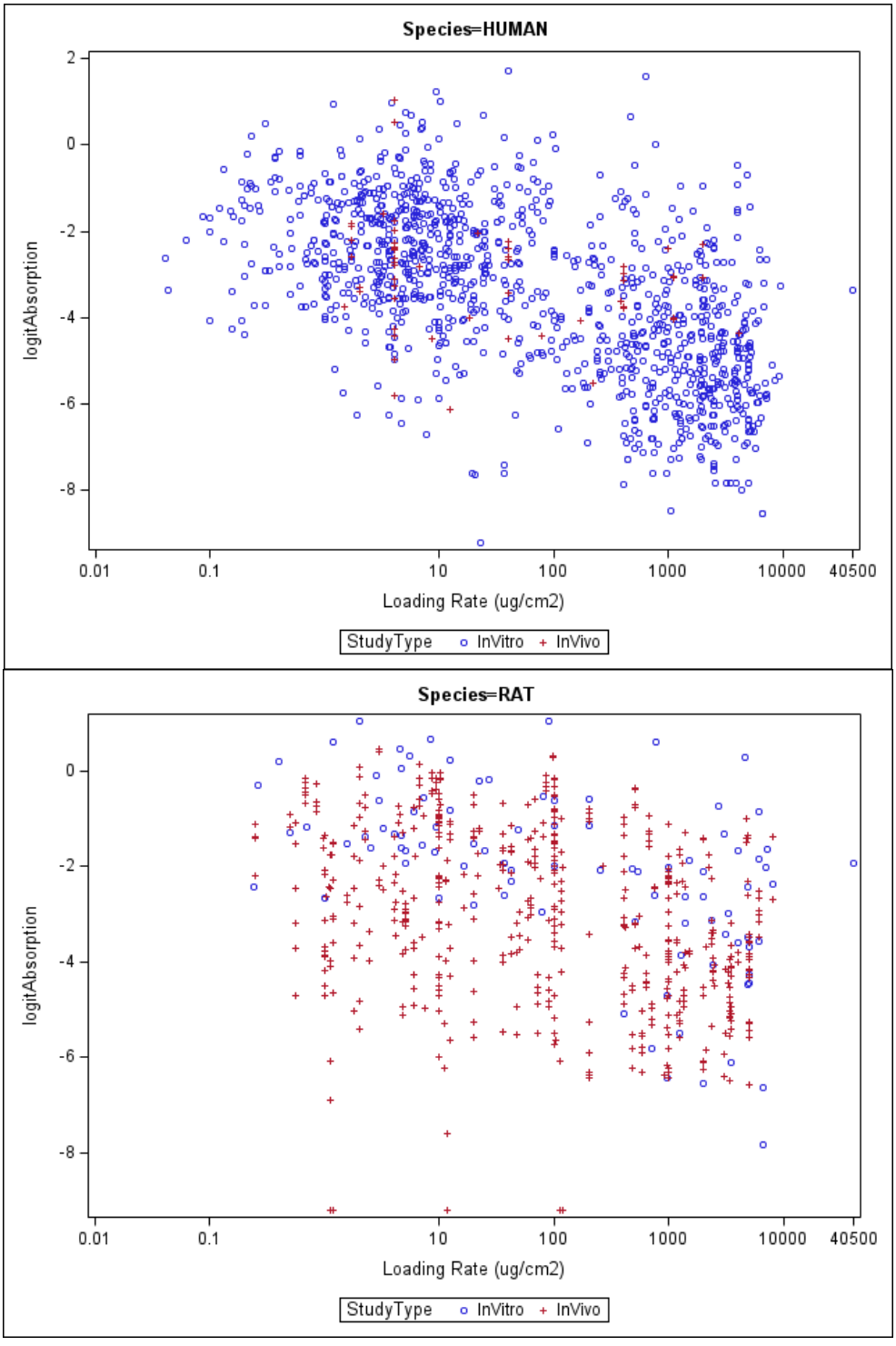
Figures A.2.5.F7- A.2.5.F8: scatterplots of logit(percent absorption) vs. exposure duration by study type using combined database



Figures A.2.5.F9- A.2.5.F10: scatterplots of percent absorption vs. loading rate by study type using combined database



Figures A.2.5.F11- A.2.5.F12: scatterplots of logit(percent absorption) vs. loading rate by study type using combined database



A.2.6 Results of Initial Analyses

Results of Analyses using EPA database– without species or study type

Table A.2.6.T5: Estimated coefficients of fixed effects in the final model using EPA database without considering species or study type

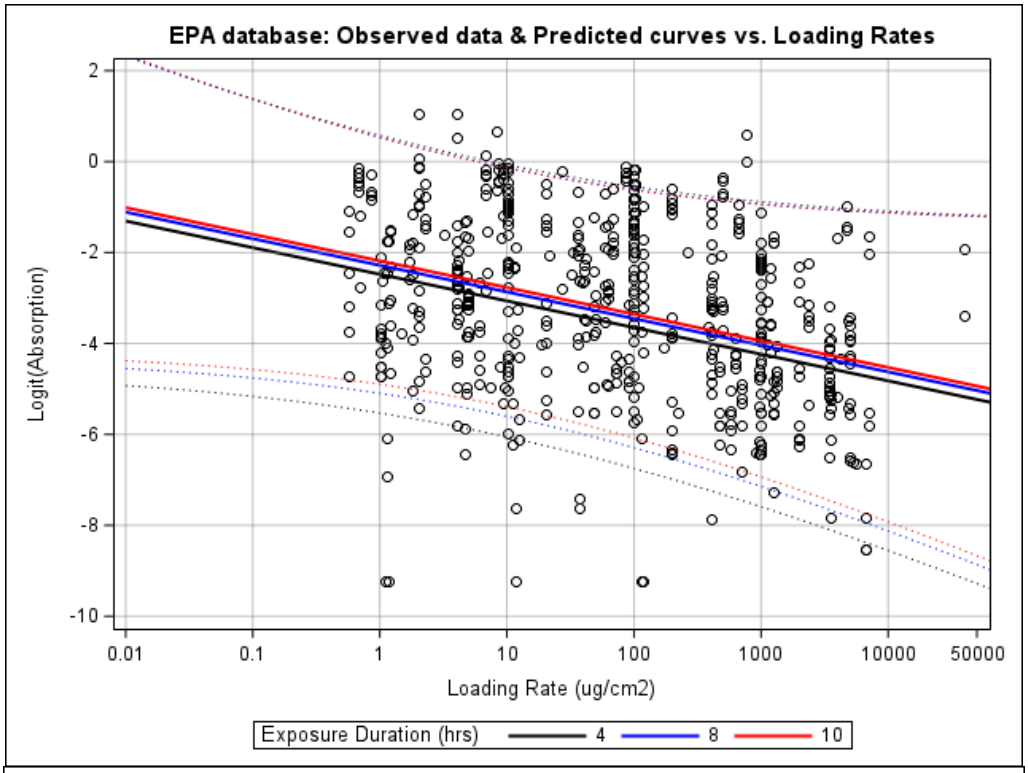
Solution for Fixed Effects								
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
Intercept	-2.6755	0.3330	36	-8.04	<.0001	0.05	-3.3507	-2.0002
logLoadRate	-0.2544	0.03843	28	-6.62	<.0001	0.05	-0.3331	-0.1757
ExpDuration	0.04920	0.01174	24	4.19	0.0003	0.05	0.02496	0.07343

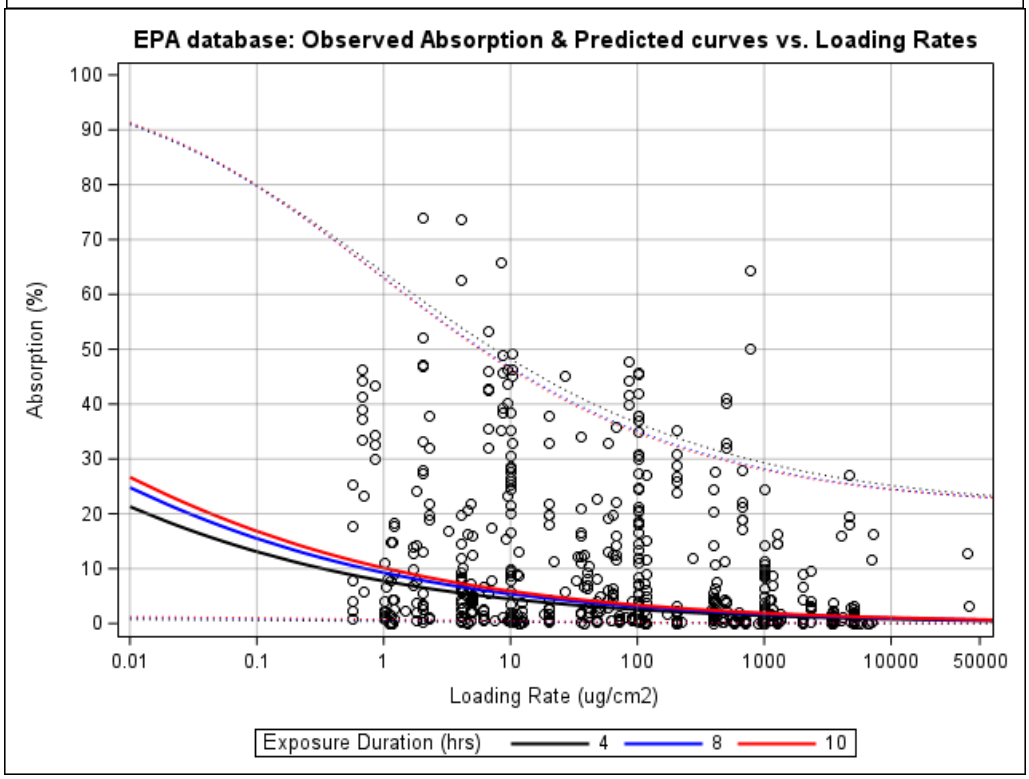
Below is the statistical equation of mean absorption (%) without random error terms of the data analysis using EPA data:

% absorption = 100 × exp(A)/{1 + exp(A)},

where A = – 2.6755 – 0.2544 × log(loading rate, $\mu g/cm^2$) + 0.0492 × exposure duration *hours*

Figures A.2.6.F13-A.2.6.F14: EPA database analysis without species or study type – estimated mean curves





Results of Analyses using EPA database – species and study type were also evaluated

Table A.2.6.T6: Estimated coefficients of fixed effects in the final model using EPA database where species and study type were also evaluated

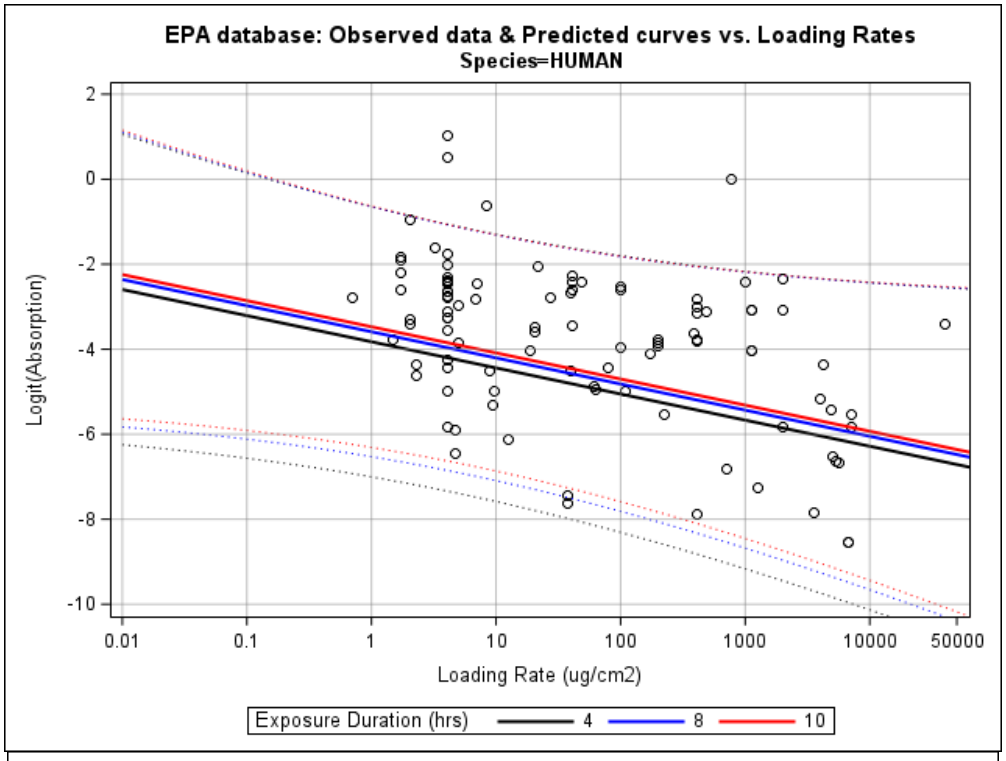
Solution for Fixed Effects									
Effect	**Species**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
Intercept		-2.0641	0.3389	36	-6.09	<.0001	0.05	-2.7514	-1.3767
logLoadRate		-0.2669	0.03565	28	-7.49	<.0001	0.05	-0.3399	-0.1939
ExpDuration		0.05879	0.01214	24	4.84	<.0001	0.05	0.03373	0.08385
Species	HUMAN	-1.9958	0.1337	477	-14.93	<.0001	0.05	-2.2586	-1.7331
Species	RAT	0	.	.	.	.	.	.	.

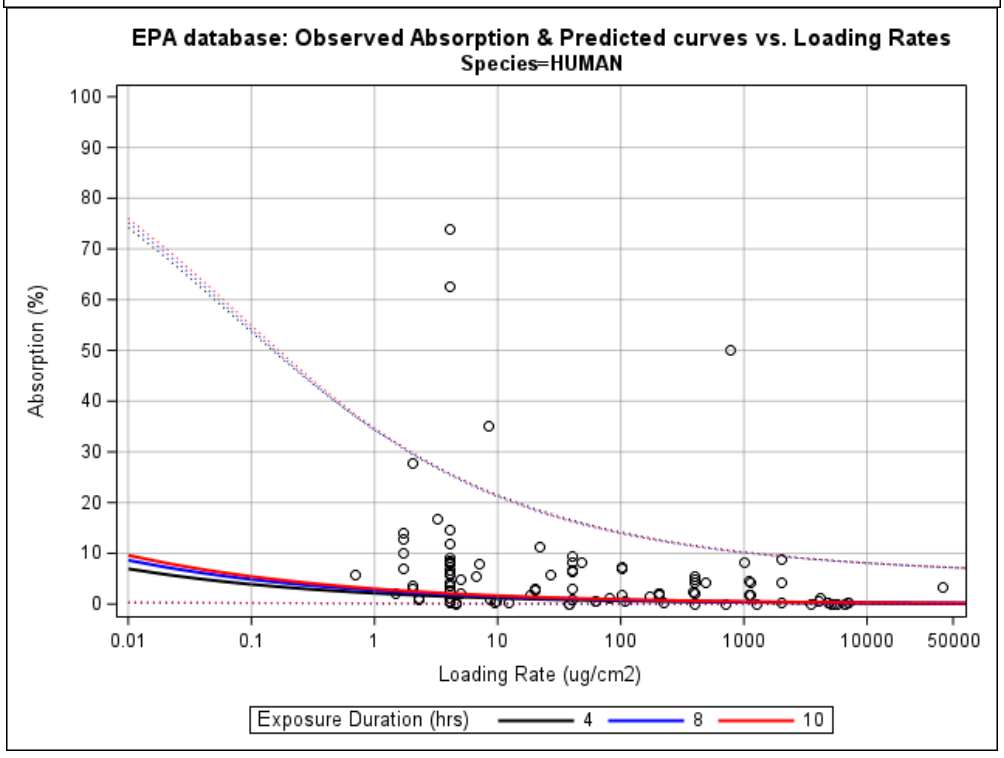
Study type was not statistically significant and was not included in the final model. Below is the statistical equation of mean absorption (%) without random error terms of the data analysis using EPA data:

% absorption = 100 × exp(A)/{1 + exp(A)},

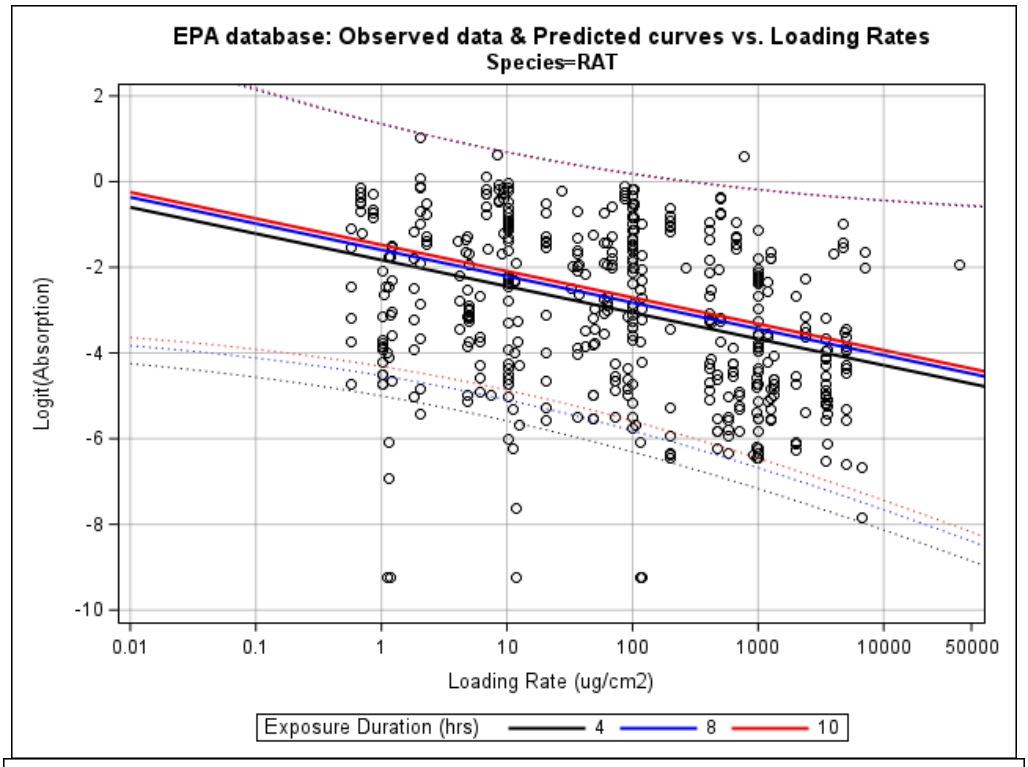
where A = – 2.0641 – 0.2699 × log(loading rate, µg/cm^2) + 0.0588 × exposure duration hours –
1.9958 × (0 if Species = rat, 1 if Species = human)

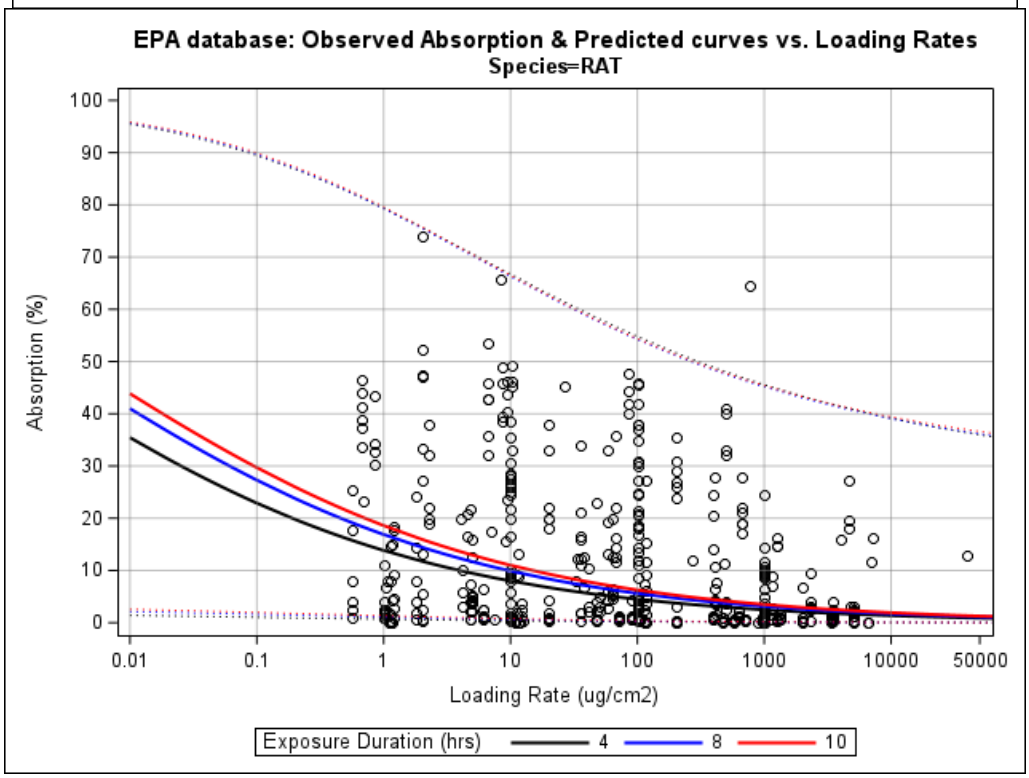
Figures A.2.6.F15-A.2.6.F16: EPA database analysis where species and study type were also evaluated – estimated mean curves of human





Figures A.2.6.F17-A.2.6.F18: EPA database analysis where species and study type were also evaluated – estimated mean curves of rat





Results of Analysis using combined database – both human and rat data

Table A.2.6.T7: Estimated coefficients of fixed effects in the final model, using combined database

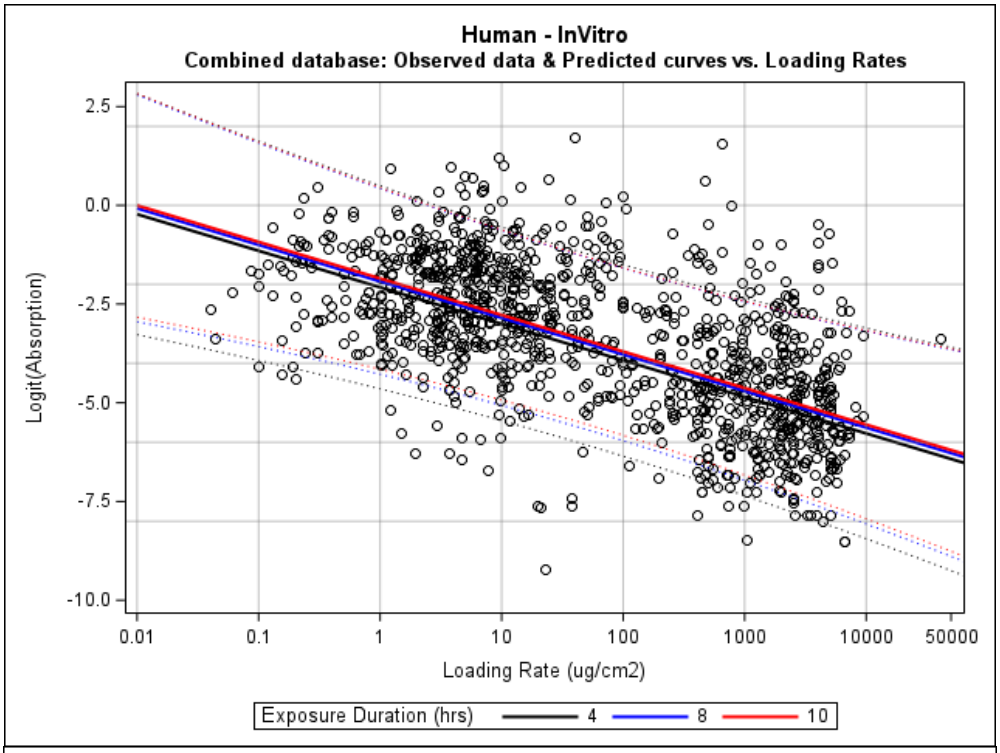
Solution for Fixed Effects										
Effect	**Species**	**Study Type**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
Intercept			-2.2254	0.1451	249	-15.34	<.0001	0.05	-2.5111	-1.9397
Species	RAT		1.6538	0.1135	1279	14.57	<.0001	0.05	1.4311	1.8765
Species	HUMAN		0	.	.	.	.	.	.	.
StudyType		InVivo	-1.7460	0.2082	1279	-8.39	<.0001	0.05	-2.1544	-1.3376
StudyType		InVitro	0	.	.	.	.	.	.	.
logLoadRate			-0.4018	0.01289	231	-31.17	<.0001	0.05	-0.4272	-0.3764
ExpDuration			0.03735	0.01142	68	3.27	0.0017	0.05	0.01457	0.06013
logLoadRate*StudyType		InVivo	0.1347	0.02317	1279	5.82	<.0001	0.05	0.08927	0.1802
logLoadRate*StudyType		InVitro	0	.	.	.	.	.	.	.
ExpDuration*StudyType		InVivo	0.05872	0.01400	1279	4.19	<.0001	0.05	0.03125	0.08619
ExpDuration*StudyType		InVitro	0	.	.	.	.	.	.	.

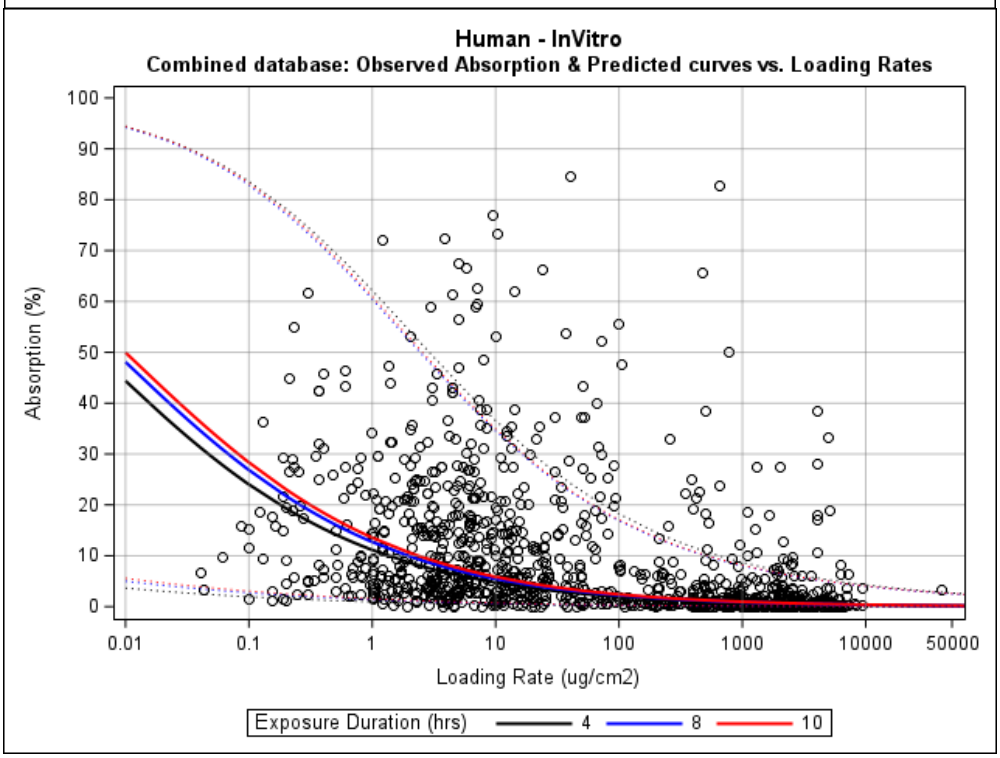
Below is the statistical equation of mean absorption (%) without random error terms of the data analysis using both rat and human data: (re-written from Table A.2.6.T5):

% absorption = 100 × exp(A)/{1 + exp(A)},

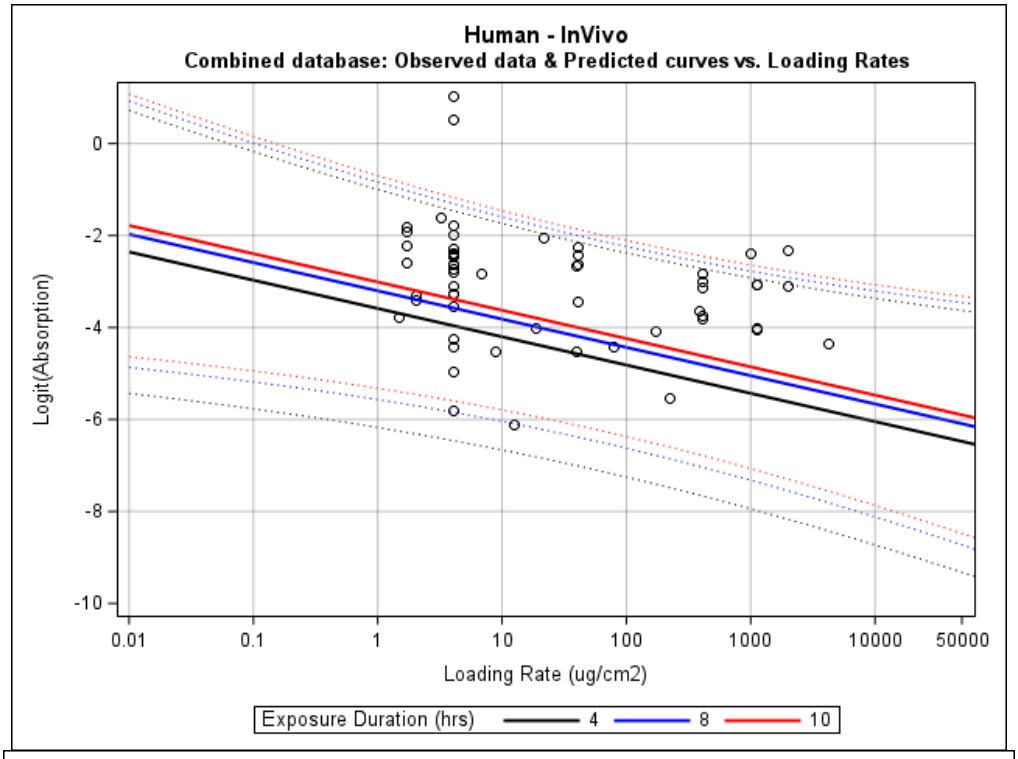
where A = – 2.2254 + 1.6538 × (0 if species = human, 1 if species = rat)
– 1.7460 × (0 if StudyType = *in vitro*, 1 if StudyType = *in vivo*)
+ 0.0374 × exposure duration *hours*
– 0.4018 × log(loading rate, $\mu g/cm^2$)
+ 0.0587 × exposure duration *hours* × (0 if StudyType = *in vitro*, 1 if StudyType = *in vivo*)
+ 0.1347 × log(loading rate $\mu g/cm^2$) × (0 if StudyType = *in vitro*, 1 if StudyType = *in vivo*)

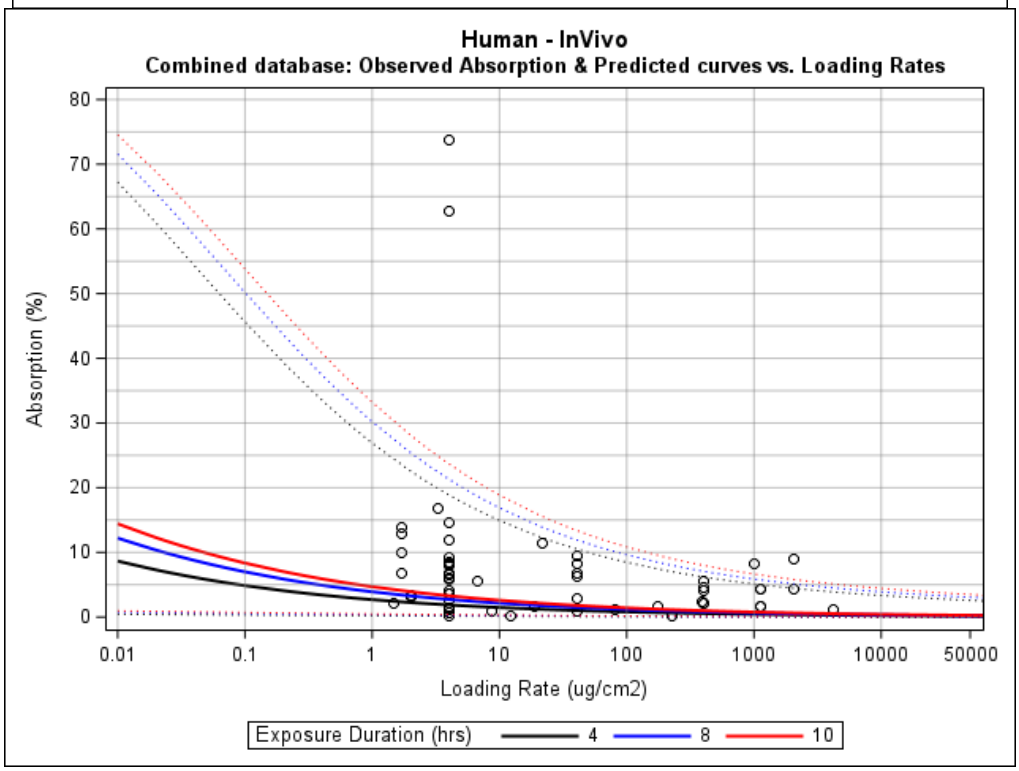
Figures A.2.6.F19- A.2.6.F20: Combined database – *in vitro* data and estimated mean curves of human



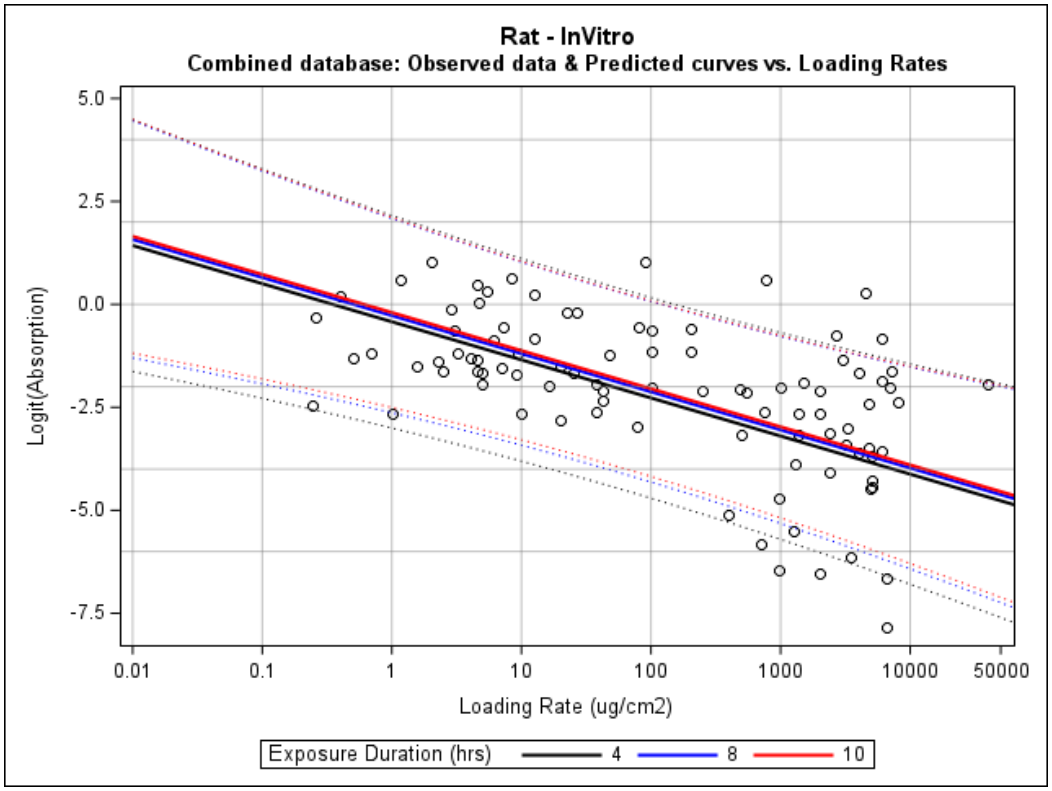


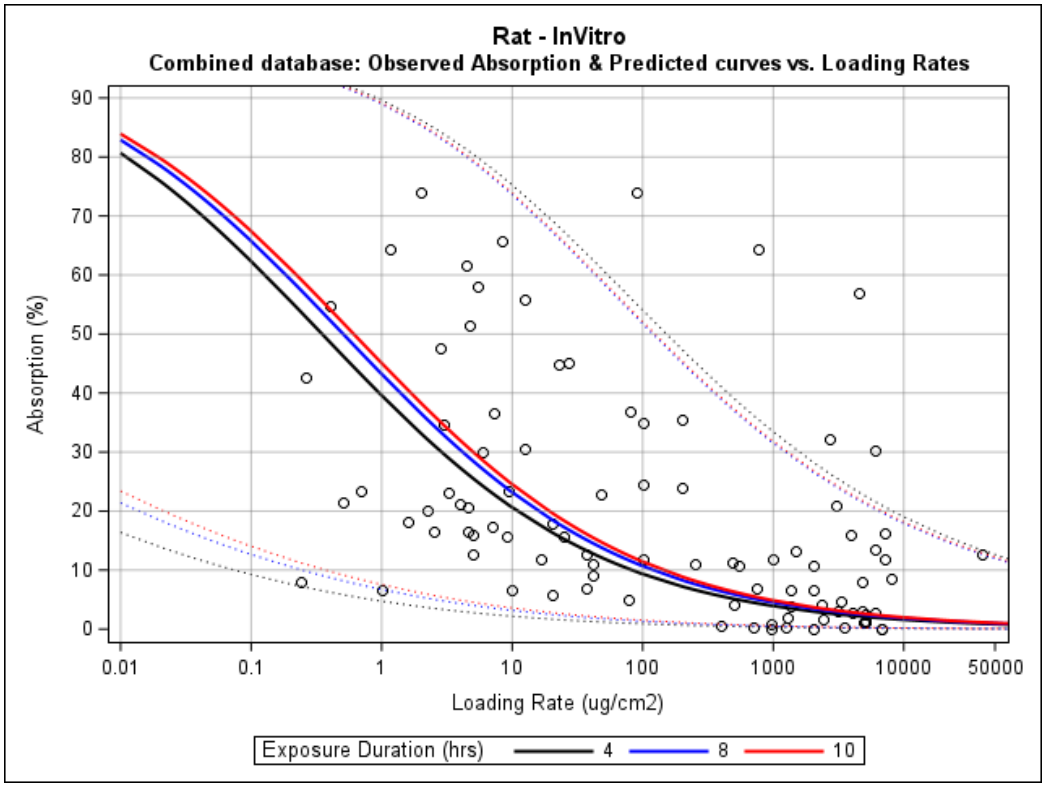
Figures A.2.6.F21- A.2.6.F22: Combined database – *in vivo* data and estimated mean curves of human



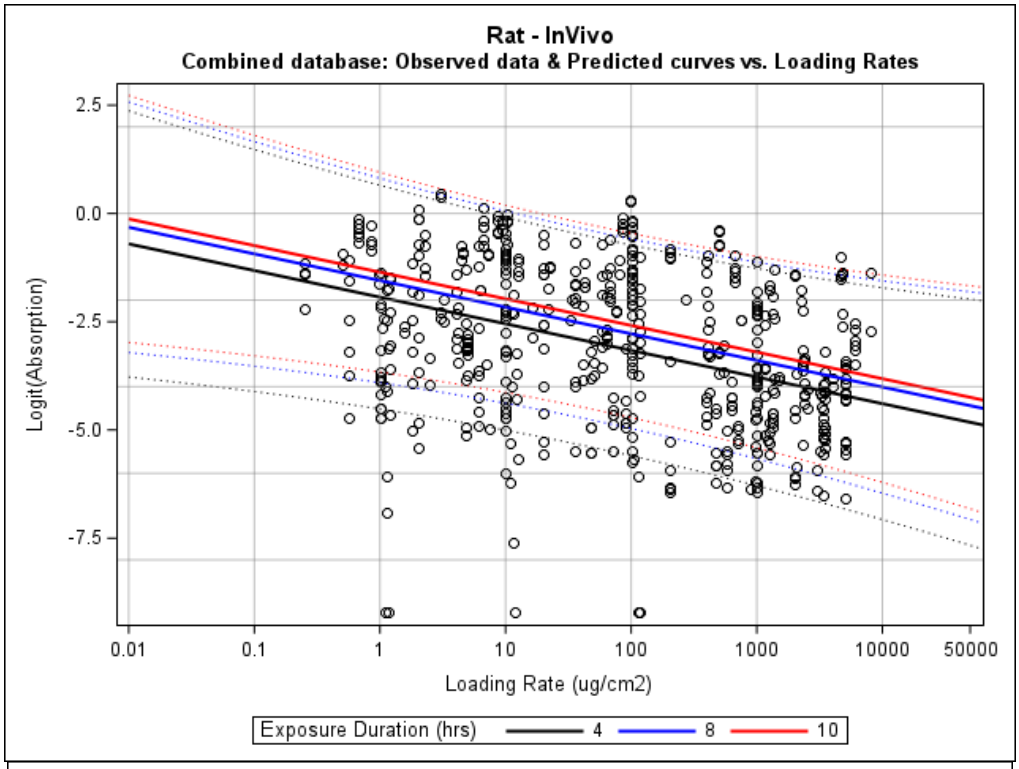


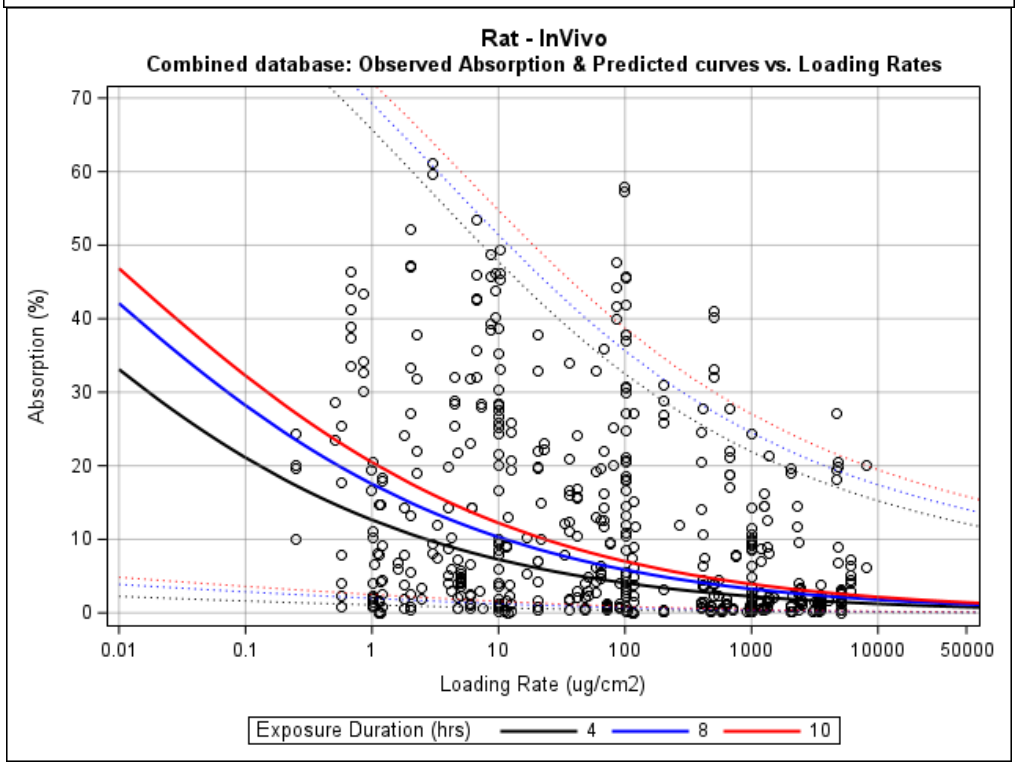
Figures A.2.6.F23- A.2.6.F24: Combined database – *in vitro* data and estimated mean curves of rat





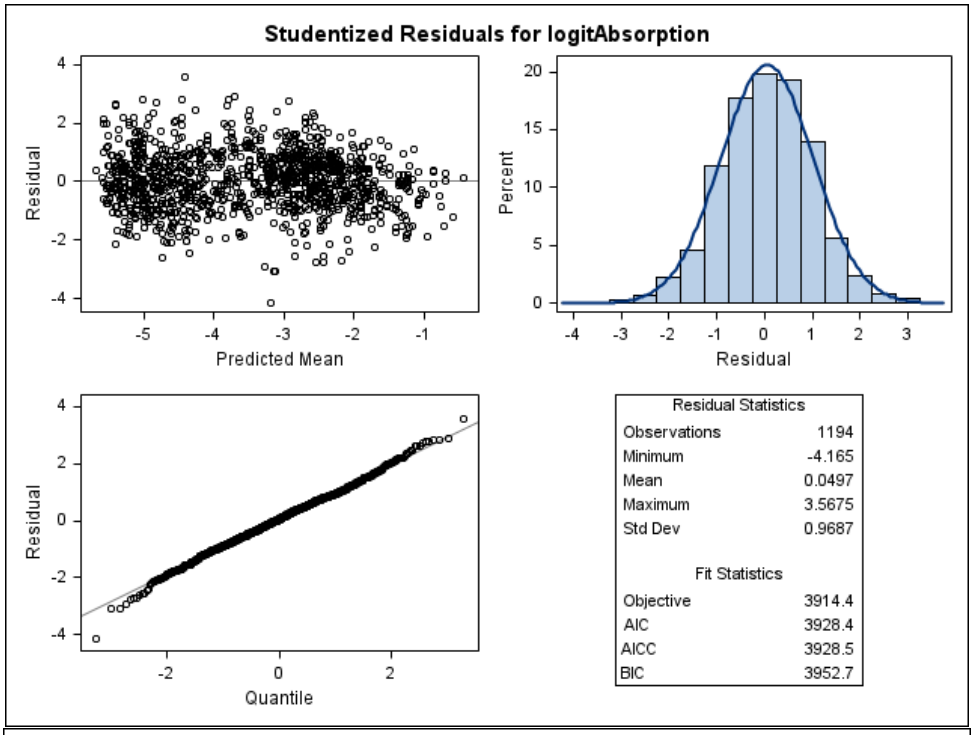
Figures A.2.6.F25- A.2.6.F26: Combined database – *in vivo* data and estimated mean curves of rat

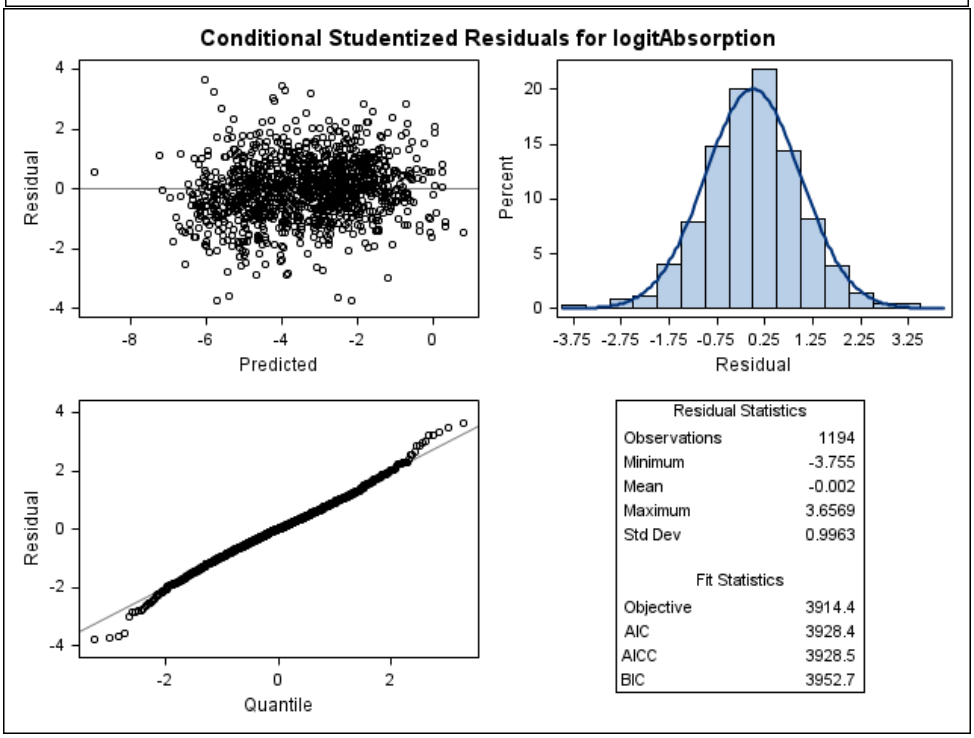




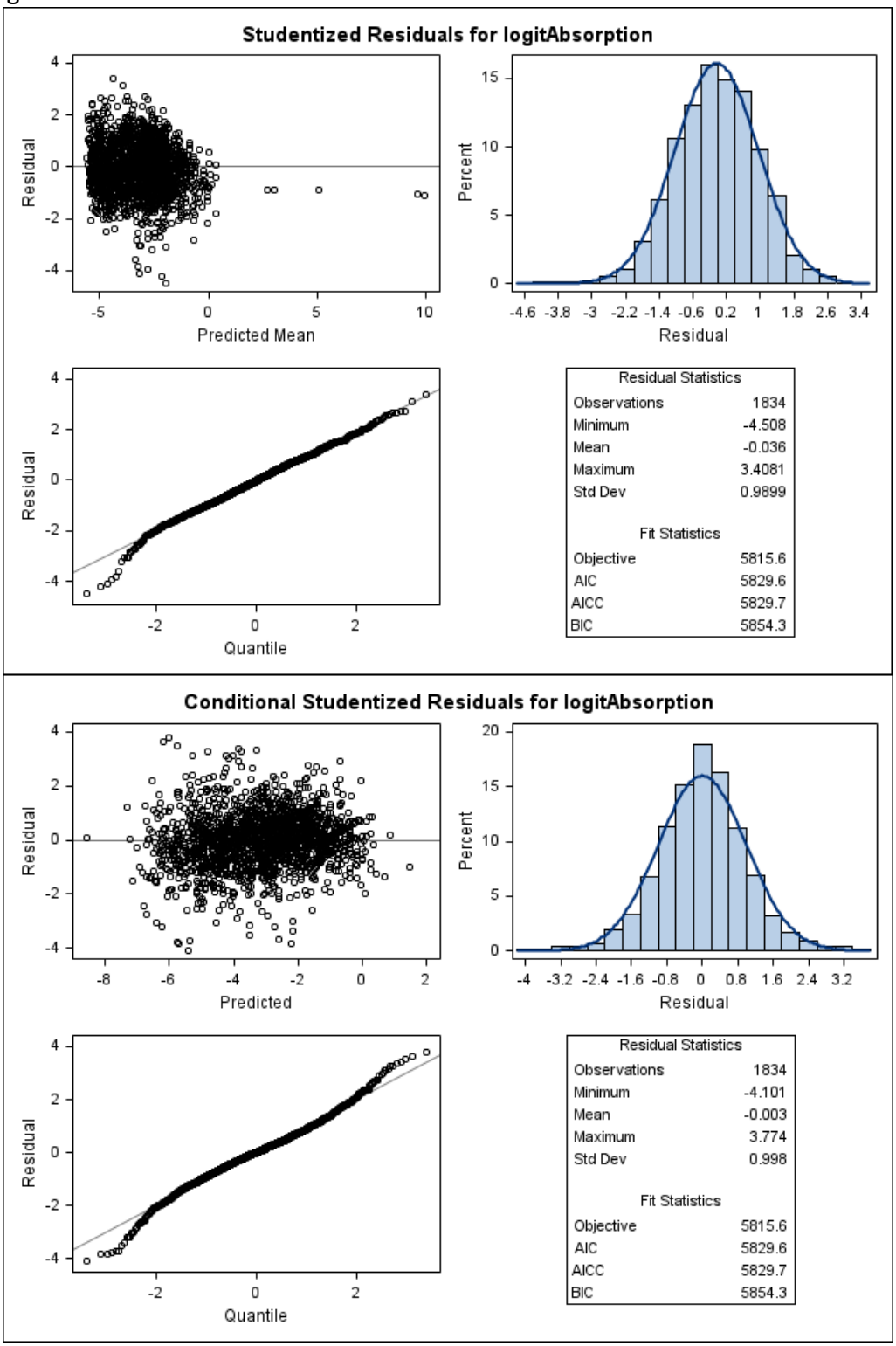
A.2.7 Model Regression Diagnostics

Figures A.2.7.F27- A.2.7.F28: Regression diagnostics of model analysis using only human data using combined database

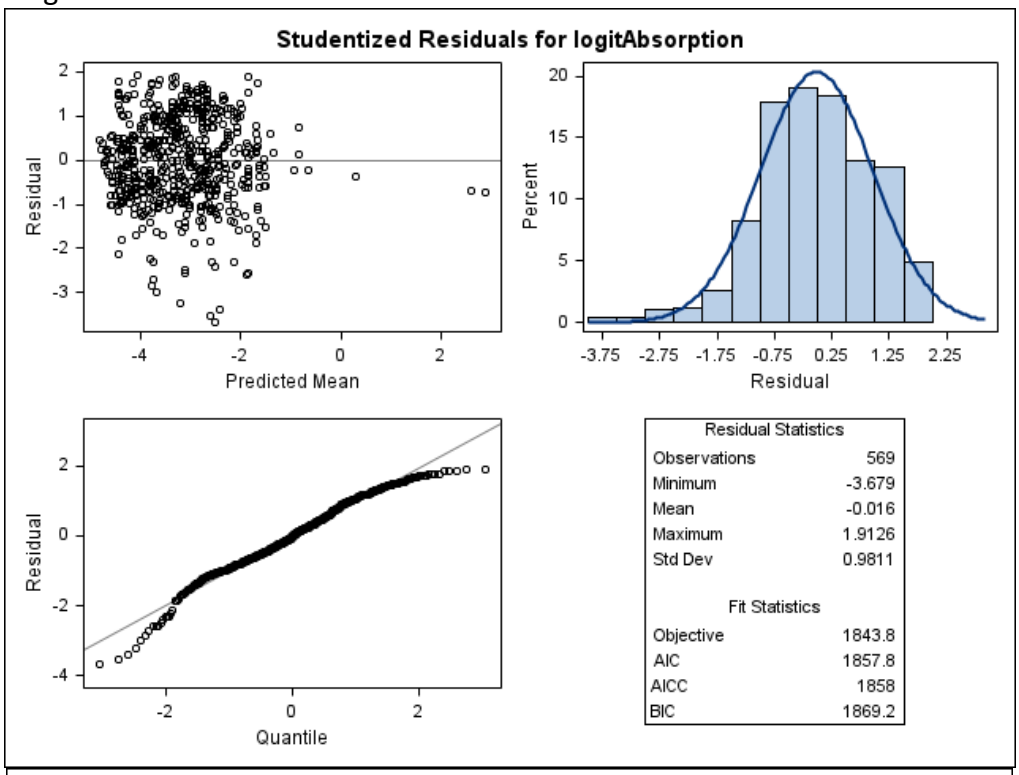


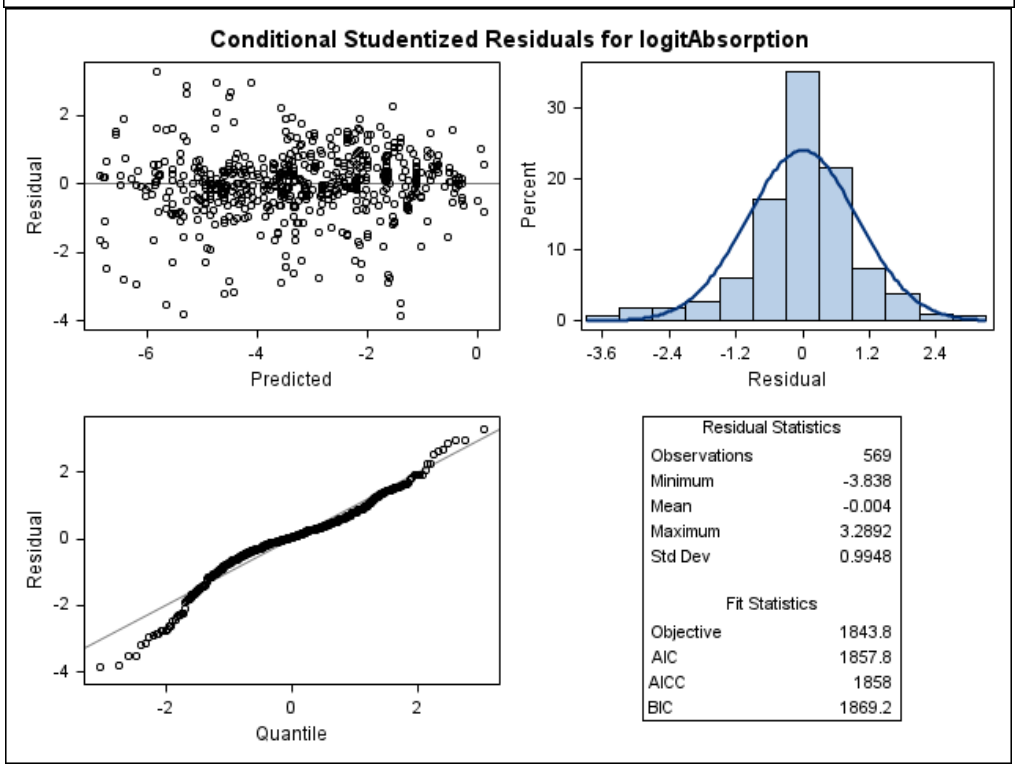


Figures A.2.7.F29- A.2.7.F30: Regression diagnostics of model analysis using both human & rat data using combined database

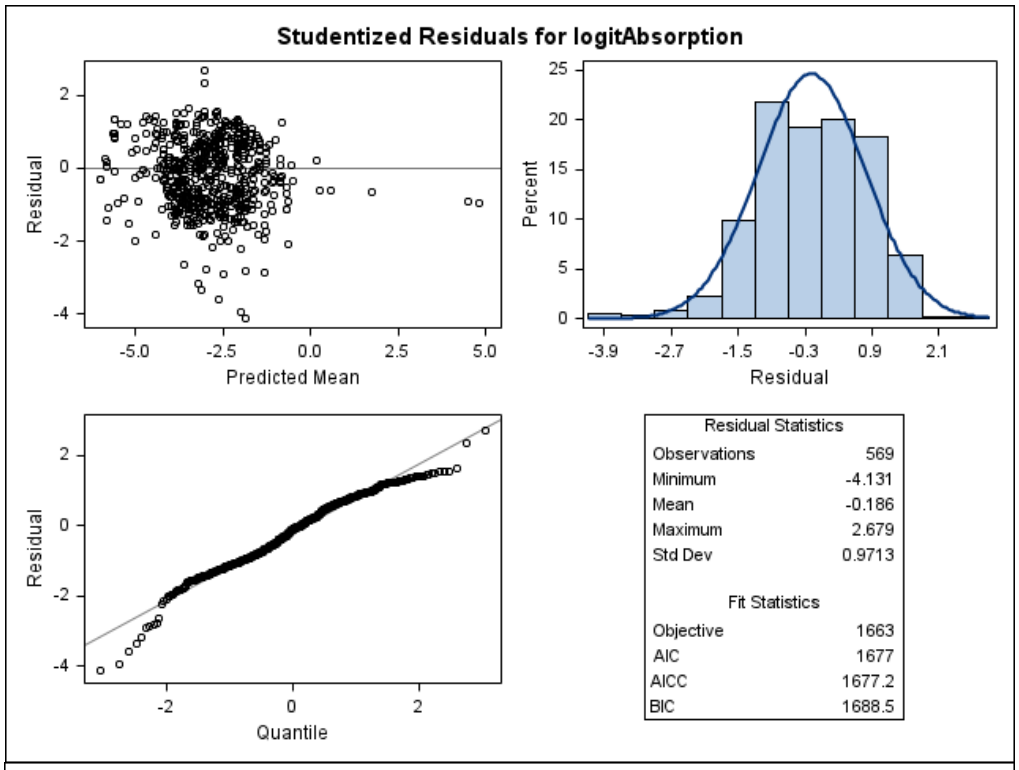


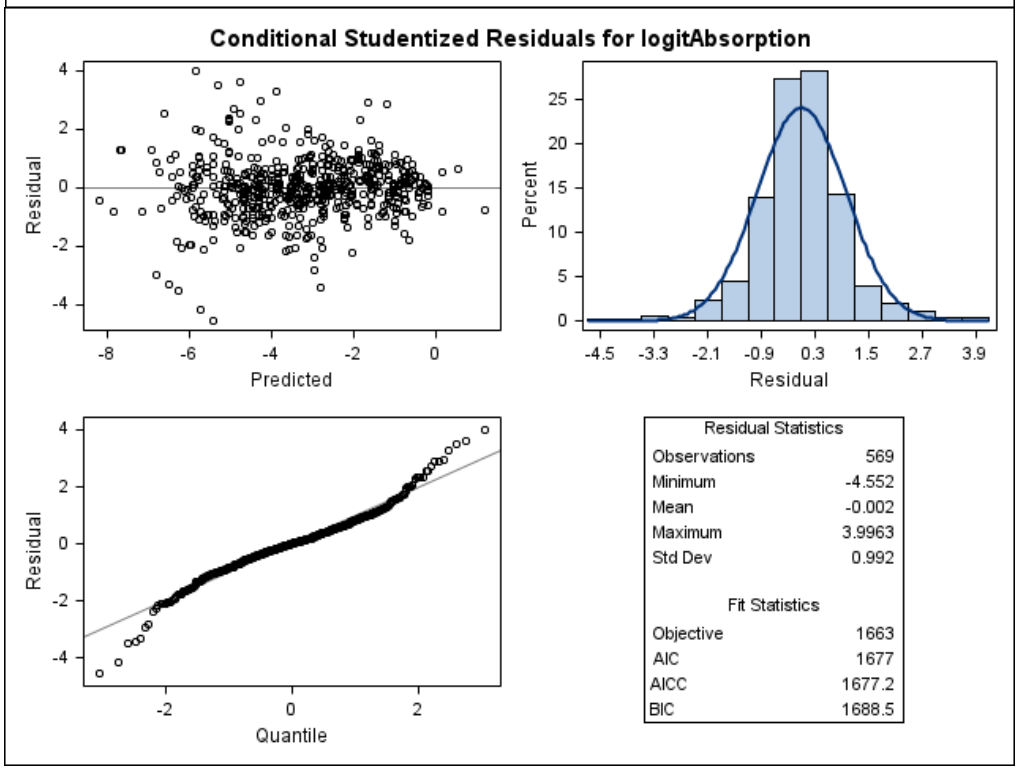
Figures A.2.7.F31- A.2.7.F32: Regression diagnostics of model analysis without Study Type or Species using EPA database





Figures A.2.7.F33- A.2.7.F34: Regression diagnostics of model analysis also including Study Type or Species using EPA database


Studentized Residuals for logitAbsorption
Residual
Predicted Mean
Percent
Residual
Residual
Quantile
Residual Statistics
Observations 569
Minimum -4.131
Mean -0.186
Maximum 2.679
Std Dev 0.9713
Fit Statistics
Objective 1663
AIC 1677
AICC 1677.2
BIC 1688.5


Conditional Studentized Residuals for logitAbsorption
Residual
Predicted
Percent
Residual
Residual
Quantile
Residual Statistics
Observations 569
Minimum -4.552
Mean -0.002
Maximum 3.9963
Std Dev 0.992
Fit Statistics
Objective 1663
AIC 1677
AICC 1677.2
BIC 1688.5

A.2.8 SAS Code

A.2.8.1 - Cleaned SAS Dataset and SAS Code files

Cleaned SAS Dataset

absorption_all.sas7bdat

SAS Files

MEA - clean and combine all databas

MEA US-EFSA-Allen 2023 data analysis 1.

A.2.8.2 - SAS Codes for Data Cleaning

```
*=========================================================================*
* Programmer: James Nguyen, USEPA                                         *
*                                                                         *
* Project: Method Efficiency Adjustment (MEA) for Pesticide Exposure      *
*          Assessment                                                     *
*                                                                         *
* Purpose: clean and combine databases into one dataset                   *
*                                                                         *
* Databases:                                                              *
*   - EPA:  "AppA_OPP_MEA_Response_010821.xlsx"                           *
*   - EFSA: "EFSA_Human in vitro dermal absorption PPPs dataset.xlsx"     *
*   - Allen et. al 2001: "triplepackfinal-allen2021-508.xlsx"             *
*                                                                         *
* Date: 11/2023                                                           *
*=========================================================================*;
Options NoDate NoNumber ps=100 ls=100 FormDlim="=";

%let dpath=C:\Users\JNGUYEN\OneDrive - Environmental Protection Agency (EPA)\MEA;
libname MEA "&dpath";


*================================> cleaning EPA database
<================================;

%let file1=AppA_OPP_MEA_Response_010821.xlsx;

libname xlsx1 "&dpath\&file1"  HEADER=NO MIXED=YES;

Data Absorption_US;
      retain Database Study Species StudyType Chemical ExpDuration LoadRate
logLoadRate Absorption logitAbsorption;
      length Database $10. Species StudyType $10. Chemical $50.;
      set xlsx1."AbsorpData$"n;

      if 1 < _N_ < 638;

      Database = 'EPA';

      Study = F2;

      Species = trim(left(upcase(F7)));

      if index(trim(left(upcase(F8))), "IN VITRO") > 0 then StudyType = "InVitro";
      else if index(trim(left(upcase(F8))), "IN VIVO") > 0 then StudyType = "InVivo";

      Chemical = trim(left(F4));

      LoadRate = input(F5,8.);
      logLoadRate = log(LoadRate);

      *====> The decisions below were made after checking with Matt and Philip;
      if F9 = "0" then F9 = "0.01";
      if F9 = "<1%" then F9 = "1";
      Absorption = input(F9, 8.);

      logitAbsorption = log(Absorption/(100-Absorption));

      ExpDuration = input(F11, 8.);
```

```
      drop F16-F63;
run;

Data Absorption_US;
      set Absorption_US;
      retain tempvar;
      if compress(Study) ^= "" then tempvar=Study;
      if compress(Study) = "" then Study = tempvar;
      drop tempvar F1-F15;
run;


/*

Data check;
      set Absorption_US;
      if absorption <= 0;
run;
Data check1;
      set Absorption_US;
      if     LoadRate = .;
run;
Data check2;
      set Absorption_US;
      if     Species = "NA";
run;

Proc freq  data = Absorption_US;
      table F8*Species/nocol nopercent norow nocum;
run;

Proc freq  data = Absorption_US;
      table StudyType StudyType*Species Chemical/nopercent nocol norow nocum;
run;


*===> Need to talk to Matt and Philip:
      - group In Vivo and In Vitro
      - set absorption = 0.01 for value = 0
      - Name of chemical
      - ExpDuration vs. Collection Time for analysis;
      ;

Proc sql;
      create table check1 as
      select distinct absorption
      from Absorption_US
      order by absorption;
quit;

Proc freq data = Absorption_US;
      table  ExpDuration /nocum norow nocol nopercent;
run;

*/


Data Absorption_US;
      set Absorption_US;
      if Absorption = . then delete;
      if LoadRate = . then delete;
```

```
       *===> only a few records of other species.  The decision below is made after
checking with Matt and Philip;
       if species not in ("HUMAN","RAT") then delete;
       if StudyType = "" then delete;

       if ExpDuration = . then delete;
run;

/*
Proc freq data = Absorption_US;
       table chemical  /nocum norow nocol nopercent;
run;
*/


Data Absorption_US;
       set Absorption_US;

       if Chemical in ("2,4-DB-DMA","2,4-dimethylamine","24-D","24-DMA","24-DMA/DEET")
then Chemical = "2,4-D";
       if Chemical = "diquat" then ChemicaL = "Diquat";
       if Chemical = "permethrin" then ChemicaL = "Permethrin";
       if Chemical in ("chlorothaloni-SC","chlorothalonil-SC","chlorothalonil-WDG")
then ChemicaL = "chlorothalonil";
       if Chemical in ("propargite - Comite","propargite - Comite II","propargite -
Omite 30W","propargite - Omite 6E")
              then Chemical ="propargite";

       if Chemical = "baygon" then delete;

       Chemical = upcase(Chemical);

Run;



*================================> cleaning EFSA database
<================================;

%let file2=EFSA_Human in vitro dermal absorption PPPs dataset.xlsx;

libname xlsx2 "&dpath\&file2"  HEADER=Yes MIXED=YES;

Data EFSA;
       set xlsx2."Dataset$"n;
       ID = compbl(trim(left(Active_substance_name__))||"---"||
                           trim(left(Study_identifier))||"---"||
                           trim(left(Formulation_type))||"---"||
                           trim(left(Exposure_duration__h_))||"---"||
                           trim(left(Applied_Concentration___g_cm2__M)));
run;

/*
Proc SQL;

       create table chem_study_StudyType as
              select distinct Active_substance_name__, Study_identifier,
Formulation_type
              from EFSA;

       create table chem_study as
              select  Active_substance_name__, Study_identifier, count(*) as n
```

```
              from chem_study_StudyType
              group by Active_substance_name__, Study_identifier;
quit;
*/

Proc SQL;
       create table Absorption_EU as
              select distinct Study_identifier as Study, Active_substance_name__ as
Chemical label = "Chemical",
                           Exposure_duration__h_ as ExpDuration label = "Exposure
Duration",
                           Applied_Concentration___g_cm2__M as LoadRate label =
"Loading Rate",
                           Absorbed__directly_absorbed_who0 as Absorption label =
"Absorption", ID
              from EFSA;

/*
       create table chemicals as
              select distinct Chemical
              from Absorption_EU;
*/

quit;

/*
ods rtf;
Proc Print data = chemicals noobs; run;
ods rtf close;
*/

Data Absorption_EU;
       retain Database Study Species StudyType Chemical ExpDuration LoadRate
logLoadRate Absorption logitAbsorption;
       length Study $255. Database Species StudyType $10. Chemical $50.;
       set Absorption_EU;


       Database = 'EFSA';
       species = "HUMAN";
       StudyType = "InVitro";

       if Absorption < 0 then delete;
       if Absorption = 0 then Absorption = 0.01;
       if LoadRate = . then delete;
       logLoadRate = log(LoadRate);

       logitAbsorption = log(Absorption/(100-Absorption));

       Chemical = trim(left(Chemical));
       if Chemical = "Cyflometofen" then Chemical = "Cyflumetofen";
       if Chemical = "Cymoxynil " then Chemical = "Cymoxanil";
       if Chemical = "pentiopyrad" then Chemical = "penthiopyrad";
       Chemical = upcase(Chemical);

       drop ID;
run;
```

```
*============================> cleaning Allen et. al 2001  database
<======================*;

/*

*==> To run below code to import Excel file, the EXCEL file must be opened;

%let file1=triplepackfinal-allen2021-508.xlsx;

x '&dpath\&file1';
filename tmp dde 'Excel|Data!r2c1:r349c12' notab;
Data Allen;
       infile tmp dlm = '09'x dsd truncover lrecl=1000 firstobs=1;
       input
              StudyType:          $20.
              Index:              $10.
              delete3:            $10.
              delete4:            $10.
              ExpDuration: best12.
              delete6:            $10.
              delete7:            $10.
              Concentration:      best12.
              Units:              $10.
              delete10:           $10.
              delete11:           $10.
              Absorption:         best12.
              ;
run;

filename tmp dde "Excel|system";

data _null_;
       file tmp;
       put '[Error(False)]';
       put '[quit()]';
run;

Data MEA.Allen;
       set Allen;
run;

*/


Data Absorption_Allen;
       retain Database Species StudyType Chemical ExpDuration LoadRate logLoadRate
Absorption logitAbsorption;
       set MEA.Allen;

       length Database Species StudyType $10. Chemical $50.;

       if index(upcase(delete4),'MAX') > 0 and StudyType = 'InVitro' then delete;

       Database = 'Allen';
       Species = upcase(scan(StudyType, 1, '_'));
       StudyType = scan(StudyType, 2, '_');

       Chemical = compress(index,,'kd');

       if StudyType = 'InVitro' then do;
              if Units = '' then delete;
              else if Units = 'g/L' then LoadRate =
((Concentration*10)/1000000)*1000000;
```

```
            else if Units = 'mg/cm2' then LoadRate = Concentration*1000;
            else if Units in('mg/mL', 'mg/ml') then LoadRate =
((Concentration*10)/1000)*1000;
            else LoadRate = Concentration;
      end;
      if StudyType = 'InVivo' then do;
            if Units = 'mg' then LoadRate = (Concentration/10)*1000;
            else if Units = 'g/L' then LoadRate =
((Concentration*10)/1000000)*1000000;
            else if Units = 'mg/10 cm2' then LoadRate = (Concentration/10)*1000;
            else if Units = 'mg/cm2' then LoadRate = Concentration*1000;
            else if Units = 'mg/mL' then LoadRate = ((Concentration*10)/1000)*1000;
            else LoadRate = Concentration;
      end;

      logLoadRate = log(LoadRate);
      logitAbsorption = log(Absorption/(100-Absorption));

      drop StudyType delete: index concentration units;
run;


*=======================> Combine all cleaned database <=======================*;


Data Absorption_ALL;
      set Absorption_US Absorption_EU Absorption_Allen;

      if Chemical = "SYN520453 (ISOPYRAZAM)" then Chemical = "ISOPYRAZAM";
      label LoadRate = 'Loading Rate (ug/cm2)' ExpDuration = 'Exposure Duration
(hrs)';
run;

/*
Proc SQL;
      create table Chemicals as
      select distinct Chemical
      from Absorption_ALL
      order by Chemical;
quit;

ods rtf;
proc print data = Chemicals noobs; run;
ods rtf close;
*/

Data MEA.Absorption_ALL;
      set Absorption_ALL;
run;
```

A.2.8.3 - SAS Code for Data Analysis

```
*=====================================================================*
* Programmer: James Nguyen, USEPA                                     *
*                                                                     *
* Project: Method Efficiency Adjustment (MEA) for Pesticide Exposure  *
*          Assessment                                                 *
*                                                                     *
* Data:          EPA database, EFSA database, and Allen 2001 database       *
*                                                                     *
* Date: 11/2023                                                       *
*=====================================================================*;
Options NoDate NoNumber ps=100 ls=100 FormDlim="=";
ods noptitle;

%let dpath=C:\Users\JNGUYEN\OneDrive - Environmental Protection Agency (EPA)\MEA;
libname MEA "&dpath";

Data Absorption_ALL;
       set MEA.Absorption_ALL;
       label Form=StudyType;
       rename Form = StudyType;
run;


Data EPA;
       set Absorption_ALL (where=(database ='EPA'));
run;




Proc means data = Absorption_ALL min max;
       var LoadRate ExpDuration;
run;

proc sort data = Absorption_ALL; by database; run;
ods rtf;
Proc means data = Absorption_ALL min max ndec=2;
       class species StudyType;
       var absorption LoadRate ExpDuration;
run;
ods rtf close;

ods rtf;
Proc tabulate data = Absorption_ALL;
       class database Species StudyType;
       table database all, species*StudyType all;
run;
ods rtf close;

Proc SQL;
       select count(*) as counts
       from (select distinct Chemical
                from Absorption_ALL);

       select Species, StudyType, count(*) as counts
       from (select distinct Species, StudyType, Chemical
                from Absorption_ALL)
       group by Species, StudyType;
quit;
```

```
*=======================>Preliminary Analyses using EPA database
<=======================*;


*==========> model without species or StudyType;

Proc freq data = EPA;
       Table Species*StudyType;
run;


Proc sort data = EPA; by Species; run;

ods rtf;
proc sgplot data = EPA;
       by species;
       scatter x = LoadRate y = absorption/group=StudyType markerattrs = (size=5);
       yaxis type = log logbase=10 logstyle=logexpand;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 10 100 1000
10000 40500);
       label Absorption = 'Absorption (%)';
run;
proc sgplot data = EPA;
       by species;
       scatter x = LoadRate y = logitabsorption/group=StudyType markerattrs =
(size=5);
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 10 100 1000
10000 40500);
run;
ods rtf close;


*=====> deterimine random effects;

*===> model 1;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
       class  Chemical;
       model logitAbsorption = logLoadRate ExpDuration ;

       random intercept logLoadRate ExpDuration/subject = Chemical type=un;
run;
*===> model 2;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
       class  Chemical;
       model logitAbsorption = logLoadRate ExpDuration ;

       random intercept logLoadRate /subject = Chemical type=un;
run;
*===> model 3;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
       class  Chemical;
       model logitAbsorption = logLoadRate ExpDuration ;
```

```
       random intercept ExpDuration/subject = Chemical type=un;
run;
*===> model 4;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
       class  Chemical;
       model logitAbsorption = logLoadRate ExpDuration ;

       random intercept   /subject = Chemical type=un;
run;


*===============> to predict values <====================;

Data LoadRate1;
       do i = 1 to 9;       LoadRate = i/100;    output;       end;   drop i;
run;
Data LoadRate2;
       do i = 1 to 9;       LoadRate = i/10;     output;       end;   drop i;
run;
Data LoadRate3;
       do LoadRate = 1 to 9;                            output;       end;
run;
Data LoadRate4;
       do LoadRate = 10 to 90 by 10;            output;       end;
run;
Data LoadRate5;
       do LoadRate = 100 to 900 by 100;  output;       end;
run;
Data LoadRate6;
       do LoadRate = 1000 to 9000 by 1000;      output;       end;
run;
Data LoadRate7;
       do LoadRate = 10000 to 100000 by 10000; output;       end;
run;


Data ToPredict;
       set LoadRate1 - LoadRate7;

       logLoadRate = log(LoadRate);
       ToPredict=1;

       Chemical = "Unknown";

       do h = 1 to 3;
              if h = 1 then ExpDuration = 4;
              if h = 2 then ExpDuration = 8;
              if h = 3 then ExpDuration = 10;

              output;
       end; *h;
       drop h ;
run;


Data EPA1;
       set EPA ToPredict;
run;

Proc datasets nolist; delete ToPredict LoadRate1 - LoadRate7; run;quit;
```

```
*===> Final model;

ods trace off;
ods rtf;
ods graphics on;
ods exclude SolutionR ClassLevels;
Proc mixed data = EPA1 plots=All;
	class  Chemical;
	model logitAbsorption = logLoadRate ExpDuration / s cl outp=outp;

	random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;
ods rtf close;

*===> change  pred values from proportions to % values (= proporton*100);

Data outp;
	set outp;
	if ToPredict = . then do;
		Pred = .;
		Lower = .;
		Upper = .;

		*=> to create figures with nice legends.  This change will NOT be used in
any analysis;
		ExpDuration = 4;
	end;

	if ToPredict = 1 then do;
		Pred_absorption = 100*exp(Pred)/(1 + exp(Pred));
		Lower_absorption = 100*exp(Lower)/(1 + exp(Lower));
		Upper_absorption = 100*exp(Upper)/(1 + exp(Upper));
		_95CI_absorption = compbl('('||trim(left(round(Lower_absorption,
0.01)))||', '||trim(left(round(Upper_absorption, 0.01)))||')');
	end;

	keep StudyType ExpDuration Absorption logitAbsorption LoadRate Pred: Lower:
Upper: _95CI: ToPredict;
run;
Proc sort data = outp; by ToPredict ExpDuration LoadRate; run;



ods rtf;
title 'EPA database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
	scatter x = LoadRate y = logitabsorption;
	styleattrs datacontrastcolors=(black blue red);
	series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
	series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
	series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
	refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
	refline -10 -8 -6 -4 -2 0 2/axis=y transparency = 0.5;
	xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
	yaxis values = (-10 to 2 by 2) label = 'Logit(Absorption)' ;
run;
title 'EPA database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
	scatter x = LoadRate y = absorption;
```

```
      styleattrs datacontrastcolors=(black blue red);
      series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
      series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
      series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
      refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
      refline 10 20 30 40 50 60 70 80 90/axis=y transparency = 0.5;
      xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
      yaxis values = (0 to 100 by 10) label = 'Absorption (%)' ;
run;
ods rtf close;




*==========> Model also considers including species or StudyType;


*=====> deterimine random effects;

*===> model 1;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
      class  Chemical Species StudyType;
      model logitAbsorption = logLoadRate ExpDuration Species StudyType
                                          Species*LogLoadRate Species*ExpDuration
                                          StudyType*logLoadRate
StudyType*ExpDuration;

      random intercept logLoadRate ExpDuration/subject = Chemical type=un;
run;
*===> model 2;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
      class  Chemical Species StudyType;
      model logitAbsorption = logLoadRate ExpDuration Species StudyType
                                          Species*LogLoadRate Species*ExpDuration
                                          StudyType*logLoadRate
StudyType*ExpDuration;

      random intercept logLoadRate /subject = Chemical type=un;
run;
*===> model 3;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
      class  Chemical Species StudyType;
      model logitAbsorption = logLoadRate ExpDuration Species StudyType
                                          Species*LogLoadRate Species*ExpDuration
                                          StudyType*logLoadRate
StudyType*ExpDuration;

      random intercept ExpDuration/subject = Chemical type=un;
run;
*===> model 4;
ods select covparms  FitStatistics  ;
Proc mixed data = EPA ;
      class  Chemical Species StudyType;
      model logitAbsorption = logLoadRate ExpDuration Species StudyType
```

```
                                                Species*LogLoadRate Species*ExpDuration
                                                StudyType*logLoadRate
StudyType*ExpDuration
                                                logLoadRate*ExpDuration;

       random intercept   /subject = Chemical type=un;
run;



*=====> determine fixed effects;

*===> model 5;
ods select tests3  FitStatistics  ;
Proc mixed data = EPA method=ml;
       class  Chemical Species StudyType;
       model logitAbsorption = logLoadRate ExpDuration Species StudyType
                                                Species*LogLoadRate Species*ExpDuration
                                                StudyType*logLoadRate
StudyType*ExpDuration
                                                logLoadRate*ExpDuration;

       random intercept logLoadRate ExpDuration/subject = Chemical type=un;
run;
*===> model 6;
ods select tests3  FitStatistics  ;
Proc mixed data = EPA method=ml;
       class  Chemical Species ;
       model logitAbsorption = logLoadRate ExpDuration Species;

       random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;


data Test;
       Dev1 = 1638.5; df1 = 9;
       Dev2 = 1647.8; df2 = 3;

       Pvalue_Test12 = 1 - probchi(-dev1+dev2,df1-df2);
run;
Proc print data = Test noobs; var P:; run;



*==============> to predict values <====================;

Data LoadRate1;
       do i = 1 to 9;      LoadRate = i/100;    output;       end;   drop i;
run;
Data LoadRate2;
       do i = 1 to 9;      LoadRate = i/10;     output;       end;   drop i;
run;
Data LoadRate3;
       do LoadRate = 1 to 9;                          output;       end;
run;
Data LoadRate4;
       do LoadRate = 10 to 90 by 10;            output;       end;
run;
Data LoadRate5;
       do LoadRate = 100 to 900 by 100;  output;       end;
run;
Data LoadRate6;
       do LoadRate = 1000 to 9000 by 1000;      output;       end;
```

```
run;
Data LoadRate7;
	do LoadRate = 10000 to 100000 by 10000; output;	end;
run;

Data ToPredict;
	set LoadRate1 - LoadRate7;

	logLoadRate = log(LoadRate);
	ToPredict=1;

	Chemical = "Unknown";
	length Species  $10.;

	do h = 1 to 3;
		if h = 1 then ExpDuration = 4;
		if h = 2 then ExpDuration = 8;
		if h = 3 then ExpDuration = 10;

		do i = 1 to 2;
			if i = 1 then Species = 'HUMAN';
			if i = 2 then Species = 'RAT';
			output;
		end; *i;
	end; *h;
	drop h i;
run;

Proc sort data = ToPredict; by Species ExpDuration LoadRate; run;


Data EPA2;
	set EPA ToPredict;
run;


Proc datasets nolist; delete ToPredict LoadRate1 - LoadRate7; run;quit;

*===> Final model;

ods trace off;
ods rtf;
ods graphics on;
ods exclude SolutionR ClassLevels;
Proc mixed data = EPA2 plots=All;
	class  Chemical Species ;
	model logitAbsorption = logLoadRate ExpDuration Species/s cl outp=outp;

	random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;
ods rtf close;

*===> change pred values from proportions to % values (= proporton*100);

Data outp;
	set outp;
	if ToPredict = . then do;
		Pred = .;
		Lower = .;
		Upper = .;

		*=> to create figures with nice legends.  This change will NOT be used in
any analysis;
```

```
              ExpDuration = 4;
       end;

       if ToPredict = 1 then do;
              Pred_absorption = 100*exp(Pred)/(1 + exp(Pred));
              Lower_absorption = 100*exp(Lower)/(1 + exp(Lower));
              Upper_absorption = 100*exp(Upper)/(1 + exp(Upper));
              _95CI_absorption = compbl('('||trim(left(round(Lower_absorption,
0.01)))||', '||trim(left(round(Upper_absorption, 0.01)))||')');
       end;

       keep Species ExpDuration Absorption logitAbsorption LoadRate Pred: Lower:
Upper: _95CI: ToPredict;
run;
Proc sort data = outp; by Species ToPredict ExpDuration LoadRate; run;

*===> plot estimated absorption values;

ods rtf;
title 'EPA database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       by Species;
       scatter x = LoadRate y = logitabsorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
       series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline -10 -8 -6 -4 -2 0 2 4/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis values = (-10 to 2 by 2)  label = 'Logit(Absorption)' ;
run;
title 'EPA database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       by Species;
       scatter x = LoadRate y = absorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
       series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline 10 20 30 40 50 60 70 80 90/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis values = (0 to 100 by 10) label = 'Absorption (%)' ;
run;
ods rtf close;




*================================================================================;
```

```
*======================> Analysis using all databases <=========================;
*================================================================================;


*==============> to create predicted values <====================;


Data LoadRate1;
       do i = 1 to 9;       LoadRate = i/100;    output;       end;   drop i;
run;
Data LoadRate2;
       do i = 1 to 9;       LoadRate = i/10;     output;       end;   drop i;
run;
Data LoadRate3;
       do LoadRate = 1 to 9;                            output;       end;
run;
Data LoadRate4;
       do LoadRate = 10 to 90 by 10;            output;       end;
run;
Data LoadRate5;
       do LoadRate = 100 to 900 by 100;  output;       end;
run;
Data LoadRate6;
       do LoadRate = 1000 to 9000 by 1000;      output;       end;
run;
Data LoadRate7;
       do LoadRate = 10000 to 100000 by 10000; output;       end;
run;


Data ToPredict;
       set LoadRate1 - LoadRate7;

       logLoadRate = log(LoadRate);
       ToPredict=1;

       Chemical = "Unknown";
       length Species StudyType  $10.;

       do h = 1 to 3;
              if h = 1 then ExpDuration = 4;
              if h = 2 then ExpDuration = 8;
              if h = 3 then ExpDuration = 10;

              do i = 1 to 2;
                     if i = 1 then Species = 'HUMAN';
                     if i = 2 then Species = 'RAT';

                     do k = 1 to 2;
                            if k = 1 then StudyType = 'InVitro';
                            if k = 2 then StudyType = 'InVivo';
                            output;
                     end; *k;
              end; *i;
       end; *h;
       drop h i k;
run;

Proc sort data = ToPredict; by Species StudyType ExpDuration LoadRate; run;

Proc datasets nolist; delete LoadRate1 - LoadRate7; run;quit;
```

```
*==================> Analysis using only Human data <============================*;

Data Absorption_ALL;
       set Absorption_ALL ToPredict;
run;
Proc sort data = Absorption_ALL; by Species StudyType ExpDuration LoadRate; run;


ods rtf;
proc sgplot data = Absorption_ALL;
       by species;
       scatter x = ExpDuration y = absorption/group=StudyType markerattrs = (size=5);
       yaxis type = log logbase=10 logstyle=logexpand;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.1 1 10 24 48 72 120);
       label Absorption = 'Absorption (%)';
run;
proc sgplot data = Absorption_ALL;
       by species;
       scatter x = ExpDuration y = logitabsorption/group=StudyType markerattrs =
(size=5);
run;
ods rtf close;
title;

ods rtf;
proc sgplot data = Absorption_ALL;
       by species;
       scatter x = LoadRate y = absorption/group=StudyType markerattrs = (size=5);
       yaxis type = log logbase=10 logstyle=logexpand;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 10 100 1000
10000 40500);
       label Absorption = 'Absorption (%)';
run;
proc sgplot data = Absorption_ALL;
       by species;
       scatter x = LoadRate y = logitabsorption/group=StudyType markerattrs =
(size=5);
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 10 100 1000
10000 40500);
run;
ods rtf close;



*======> deterimine random effects;

*===> model 1;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL(where=(Species = 'HUMAN'));
       class Chemical StudyType ;
       model logitAbsorption = StudyType logLoadRate ExpDuration
                                                 StudyType*logLoadRate
StudyType*ExpDuration logLoadRate*ExpDuration;
       random intercept logLoadRate ExpDuration/subject = Chemical type=un;
run;
*===> model 2;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL(where=(Species = 'HUMAN'));
       class Chemical StudyType ;
       model logitAbsorption = StudyType logLoadRate ExpDuration
                                                 StudyType*logLoadRate
StudyType*ExpDuration logLoadRate*ExpDuration;
```

```
       random intercept logLoadRate /subject = Chemical type=un;
run;
*===> model 3;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL(where=(Species = 'HUMAN'));
       class Chemical StudyType ;
       model logitAbsorption = StudyType logLoadRate ExpDuration
                                                  StudyType*logLoadRate
StudyType*ExpDuration logLoadRate*ExpDuration;
       random intercept ExpDuration/subject = Chemical type=un;
run;
*===> model 4;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL(where=(Species = 'HUMAN'));
       class Chemical StudyType ;
       model logitAbsorption = StudyType logLoadRate ExpDuration
                                                  StudyType*logLoadRate
StudyType*ExpDuration logLoadRate*ExpDuration;
       random intercept   /subject = Chemical type=un;
run;



*====> determine fixed effects;
* model 1;
ods select covparms  FitStatistics  tests3;
Proc mixed data = Absorption_ALL(where=(Species = 'HUMAN')) method=ml;
       class Chemical StudyType ;
       model logitAbsorption = StudyType logLoadRate ExpDuration
                                                  StudyType*logLoadRate
StudyType*ExpDuration logLoadRate*ExpDuration;
       random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;

* model 2;
ods select covparms  FitStatistics  tests3;
Proc mixed data = Absorption_ALL(where=(Species = 'HUMAN')) method=ml;
       class Chemical StudyType ;
       model logitAbsorption = StudyType logLoadRate ExpDuration
StudyType*logLoadRate;
       random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;

data Test;
       Dev1 = 3892.1; df1 = 6;
       Dev2 = 3893.9; df2 = 4;

       Pvalue_Test12 = 1 - probchi(-dev1+dev2,df1-df2);
run;
Proc print data = Test noobs; var P:; run;



*====> Final model;

ods trace off;
ods rtf;
ods graphics on;
ods exclude SolutionR ClassLevels;
Proc mixed data = Absorption_ALL(where=(Species = 'HUMAN')) plots=All;
       class  Chemical StudyType(ref='InVitro');
```

```
	model logitAbsorption = StudyType logLoadRate ExpDuration StudyType*logLoadRate
/ s cl outp=outp;

	random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;
ods rtf close;

*===> change pred values from proportions to % values (= proporton*100);
Data outp;
	set outp;
	if ToPredict = . then do;
		Pred = .;
		Lower = .;
		Upper = .;

		*=> to create figures with nice legends.  This change will NOT be used in
any analysis;
		ExpDuration = 4;
	end;

	if ToPredict = 1 then do;
		Pred_absorption = 100*exp(Pred)/(1 + exp(Pred));
		Lower_absorption = 100*exp(Lower)/(1 + exp(Lower));
		Upper_absorption = 100*exp(Upper)/(1 + exp(Upper));
		_95CI_absorption = compbl('('||trim(left(round(Lower_absorption,
0.01)))||', '||trim(left(round(Upper_absorption, 0.01)))||')');
	end;

	keep StudyType ExpDuration Absorption logitAbsorption LoadRate Pred: Lower:
Upper: _95CI: ToPredict;
run;
Proc sort data = outp; by ToPredict ExpDuration LoadRate StudyType; run;

Proc transpose data = outp(where=(Pred ^=.)) out=outp1(drop=_NAME_) suffix=_Pred;
	by ExpDuration LoadRate;
	var Pred_absorption;
	ID StudyType;
run;
Proc transpose data = outp(where=(Pred ^=.)) out=outp2(drop=_NAME_) suffix=_95CI;
	by ExpDuration LoadRate;
	var _95CI_absorption;
	ID StudyType;
run;

Data outp_print;
	retain ExpDuration LoadRate INVITRO_Pred INVITRO_95CI INVIVO_Pred INVIVO_95CI;
	merge outp1 outp2 ;
	by ExpDuration LoadRate;
run;



ods rtf bodytitle;
title "predicted values for HUMAN - IN VITRO";
Proc print data = outp_print(where=(LoadRate<=1000)) noobs;
	format INVITRO_Pred INVIVO_Pred 6.2;
run;



*===> plot estimated absorption values;

Proc sort data = outp; by ToPredict ExpDuration StudyType LoadRate; run;
```

```
ods rtf;
title1 'Human - InVitro';
title2 'Combined database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where StudyType = "InVitro";
       scatter x = LoadRate y = logitabsorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
       series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline -8 -6 -4 -2 0 2 4/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis label = 'Logit(Absorption)' ;
run;
title2 'Combined database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where StudyType = "InVitro";
       scatter x = LoadRate y = absorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
       series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline 10 20 30 40 50 60 70 80 90/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis values = (0 to 90 by 10) label = 'Absorption (%)' ;
run;

title1 'Human - InVivo';
title2 'Combined database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where StudyType = "InVivo";
       scatter x = LoadRate y = logitabsorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
       series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline -8 -6 -4 -2 0 2/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis label = 'Logit(Absorption)' ;
run;
title2 'Combined database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where StudyType = "InVivo";
       scatter x = LoadRate y = absorption;
       styleattrs datacontrastcolors=(black blue red);
```

```
      series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
      series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
      series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
      refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
      refline 0 10 20 30 40 50 60 70 80 /axis=y transparency = 0.5;
      xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
      yaxis values = (0 to 80 by 10) label = 'Absorption (%)' ;
run;

ods rtf close;



*===> create table of predicted amount remained on skin;

*==============> to predict values <==================;

Data LoadRate1;
      do i = 1 to 100;    LoadRate = i/1000;  output;      end;   drop i;
run;
Data LoadRate2;
      do i = 105 to 500 by 5;    LoadRate = i/1000;  output;      end;   drop i;
run;
Data LoadRate3;
      do i = 510 to 1000 by 10;  LoadRate = i/1000;  output;      end;   drop i;
run;
Data LoadRate4;
      do i = 1050 to 10000 by 50;      LoadRate = i/1000;  output;      end;   drop
i;
run;
Data LoadRate5;
      do i = 10100 to 20000 by 100;    LoadRate = i/1000;  output;      end;   drop
i;
run;


Data ToPredict;
      set LoadRate1 - LoadRate5;

      logLoadRate = log(LoadRate);
      ToPredict=1;

      Chemical = "Unknown";
      length Species StudyType  $10.;
      Species = 'HUMAN';

      do h = 1 to 3;
            if h = 1 then ExpDuration = 4;
            if h = 2 then ExpDuration = 8;
            if h = 3 then ExpDuration = 10;

            StudyType = 'InVitro';
            output;
      end; *h;
      drop h k ;
run;

Proc sort data = ToPredict; by Species StudyType ExpDuration LoadRate; run;
```

```
Proc datasets nolist; delete LoadRate:; run;quit;

*===> Human data only;

Data Absorption_ALL_HUMAN;
	set MEA.Absorption_ALL;
	if Species = 'HUMAN';
run;

Data Absorption_ALL_HUMAN;
	set Absorption_ALL_HUMAN ToPredict;
run;

*===> using the final model;

ods exclude SolutionR ClassLevels;
Proc mixed data = Absorption_ALL_HUMAN plots=All;
	class  Chemical StudyType(ref='InVitro');
	model logitAbsorption = StudyType logLoadRate ExpDuration StudyType*logLoadRate
/ s cl outp=outp;

	random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;

*===> change pred values from proportions to % values (= proporton*100);
Data outp;
	set outp;
	if ToPredict = . then delete;
	if ToPredict = 1 then do;
		Pred_absorption = 100*exp(Pred)/(1 + exp(Pred));
		Lower_absorption = 100*exp(Lower)/(1 + exp(Lower));
		Upper_absorption = 100*exp(Upper)/(1 + exp(Upper));

		Pred_Remained_Amount = LoadRate*(100-Pred_absorption)/100;
		Lower_Remained_Amount = LoadRate*(100-Upper_absorption)/100;
		Upper_Remained_Amount = LoadRate*(100-Lower_absorption)/100;

		Pred_Factor = LoadRate/Pred_Remained_Amount;
		Pred_Factor_Lower = LoadRate/Upper_Remained_Amount;
		Pred_Factor_Upper = LoadRate/Lower_Remained_Amount;
	end;

	keep StudyType ExpDuration LoadRate Pred_: Lower_: Upper_:;
run;
Proc sort data = outp; by ExpDuration LoadRate StudyType; run;

Proc export data = outp
	outfile = "&dpath\Loading Rate, Predicted Amount Remainend on Skin, and
Predicted Factor.xlsx"
	dbms=xlsx
	replace;
run;

/*
ods rtf;
title1 'Human - InVitro';
Proc sgplot data = outp ;
	by ExpDuration;
	where StudyType = "InVitro";
	styleattrs datacontrastcolors=(black blue red);
	series x = LoadRate y = Pred_Remained_Amount /  SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=0.1);
```

```
      series x = LoadRate y = Lower_Remained_Amount /  SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
      series x = LoadRate y = Upper_Remained_Amount /  SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
      refline 0.01 0.1 1 10 15 20/axis = x transparency = 0.5;

      xaxis type = log logbase=10 logstyle=logexpand values=(0.001 0.01 1 10 15 20)
label='Loading Rate (ug/cm2)';
      yaxis type = log logbase=10 logstyle=logexpand label = 'Pred Remained Amount' ;
run;
ods rtf close;
*/



*==================> Analysis using both Human + Rat data
<===========================*;


*=====> deterimine random effects;

*===> model 1;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL;
      class Species Chemical StudyType ;
      model logitAbsorption = Species StudyType logLoadRate ExpDuration
                                          Species*StudyType Species*LogLoadRate
Species*ExpDuration
                                          StudyType*logLoadRate
StudyType*ExpDuration
                                          logLoadRate*ExpDuration;
      random intercept logLoadRate ExpDuration/subject = Chemical type=un;
run;
*===> model 2;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL;
      class Species Chemical StudyType ;
      model logitAbsorption = Species StudyType logLoadRate ExpDuration
                                          Species*StudyType Species*LogLoadRate
Species*ExpDuration
                                          StudyType*logLoadRate
StudyType*ExpDuration
                                          logLoadRate*ExpDuration;
      random intercept logLoadRate /subject = Chemical type=un;
run;
*===> model 3;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL;
      class Species Chemical StudyType ;
      model logitAbsorption = Species StudyType logLoadRate ExpDuration
                                          Species*StudyType Species*LogLoadRate
Species*ExpDuration
                                          StudyType*logLoadRate
StudyType*ExpDuration
                                          logLoadRate*ExpDuration;
      random intercept ExpDuration/subject = Chemical type=un;
run;
*===> model 4;
ods select covparms  FitStatistics  ;
Proc mixed data = Absorption_ALL;
      class Species Chemical StudyType ;
      model logitAbsorption = Species StudyType logLoadRate ExpDuration
```

```
                                                Species*StudyType Species*LogLoadRate
Species*ExpDuration
                                                StudyType*logLoadRate
StudyType*ExpDuration
                                                logLoadRate*ExpDuration;
      random intercept   /subject = Chemical type=un;
run;



*====> determine fixed effects;
* model 1;
ods select covparms  FitStatistics  tests3;
Proc mixed data = Absorption_ALL method=ml;
      class Species Chemical StudyType ;
      model logitAbsorption = Species StudyType logLoadRate ExpDuration
                                                Species*StudyType Species*LogLoadRate
Species*ExpDuration
                                                StudyType*logLoadRate
StudyType*ExpDuration
                                                logLoadRate*ExpDuration;
      random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;
* model 2;
ods select covparms  FitStatistics  tests3;
Proc mixed data = Absorption_ALL method=ml;
      class Species Chemical StudyType ;
      model logitAbsorption = Species StudyType logLoadRate ExpDuration
                                                StudyType*logLoadRate
StudyType*ExpDuration;
      random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;
data Test;
      Dev1 = 5777.1; df1 = 10;
      Dev2 = 5780.0; df2 = 6;

      Pvalue_Test12 = 1 - probchi(-dev1+dev2,df1-df2);
run;
Proc print data = Test noobs; var P:; run;



*====> Final model;

ods trace off;
ods rtf;
ods graphics on;
ods exclude SolutionR ClassLevels;
Proc mixed data = Absorption_ALL plots=All;
      class Species(ref='HUMAN') Chemical StudyType(ref='InVitro');
      model logitAbsorption = Species StudyType logLoadRate ExpDuration
                                                StudyType*logLoadRate
StudyType*ExpDuration / s cl outp=outp;

      random intercept logLoadRate ExpDuration /subject = Chemical type=un;
run;
ods rtf close;

*===> change pred values from proportions to % values (= proporton*100);

Data outp;
      set outp;
```

```
	if ToPredict = . then do;
		Pred = .;
		Lower = .;
		Upper = .;

		*=> to create figures with nice legends.  This change will NOT be used in
any analysis;
		ExpDuration = 4;
	end;

	if ToPredict = 1 then do;
		Pred_absorption = 100*exp(Pred)/(1 + exp(Pred));
		Lower_absorption = 100*exp(Lower)/(1 + exp(Lower));
		Upper_absorption = 100*exp(Upper)/(1 + exp(Upper));
		 _95CI_absorption = compbl('('||trim(left(round(Lower_absorption,
0.01)))||', '||trim(left(round(Upper_absorption, 0.01)))||')');
	end;

	Species_StudyType=compress(Species||'-'||StudyType);

	keep Species StudyType Species_StudyType ExpDuration Absorption logitAbsorption
LoadRate Pred: Lower: Upper: _95CI: ToPredict;
run;
Proc sort data = outp; by ToPredict ExpDuration LoadRate Species_StudyType; run;

Proc transpose data = outp(where=(Pred ^=.)) out=outp1(drop=_NAME_) suffix=_Pred;
	by ExpDuration LoadRate;
	var Pred_absorption;
	ID Species_StudyType;
run;
Proc transpose data = outp(where=(Pred ^=.)) out=outp2(drop=_NAME_) suffix=_95CI;
	by ExpDuration LoadRate;
	var _95CI_absorption;
	ID Species_StudyType;
run;

Data outp_print;
	retain ExpDuration LoadRate
		HUMAN_InVitro_Pred HUMAN_InVitro_95CI
		HUMAN_InVivo_Pred HUMAN_InVivo_95CI
		RAT_InVitro_Pred RAT_InVitro_95CI
		RAT_InVivo_Pred RAT_InVivo_95CI;
	merge outp1 outp2 ;
	by ExpDuration LoadRate;

	label HUMAN_InVitro_Pred = 'Human InVitro' HUMAN_InVitro_95CI = 'Human InVitro'
		HUMAN_InVivo_Pred = 'Human InVivo' HUMAN_InVivo_95CI = 'Human
InVivo'
		RAT_InVitro_Pred = 'Rat InVitro' RAT_InVitro_95CI ='Rat InVitro'
		RAT_InVivo_Pred = 'Rat InVivo' RAT_InVivo_95CI = 'Rat InVivo';
run;


option orientation = landscape;
ods rtf bodytitle;
title "predicted values for HUMAN - IN VITRO";
Proc print data = outp_print(where=(LoadRate<=1000)) noobs label;
	format HUMAN_InVitro_Pred HUMAN_InVivo_Pred RAT_InVitro_Pred RAT_InVivo_Pred
6.2;
run;
ods rtf close;
```

```
*===> plot estimated absorption values;

Proc sort data = outp; by Species StudyType ToPredict ExpDuration LoadRate; run;


ods rtf;
title1 'Human - InVitro';
title2 'Combined database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where species = 'HUMAN' and StudyType = "InVitro";
       scatter x = LoadRate y = logitabsorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
       series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline -8 -6 -4 -2 0 2 4/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis label = 'Logit(Absorption)' ;
run;
title2 'Combined database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where species = 'HUMAN' and StudyType = "InVitro";
       scatter x = LoadRate y = absorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
       series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline 10 20 30 40 50 60 70 80 90/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis values = (0 to 100 by 10) label = 'Absorption (%)' ;
run;

title1 'Human - InVivo';
title2 'Combined database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where species = 'HUMAN' and StudyType = "InVivo";
       scatter x = LoadRate y = logitabsorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
       series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline -8 -6 -4 -2 0 2/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis label = 'Logit(Absorption)' ;
run;
```

```
title2 'Combined database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where species = 'HUMAN' and StudyType = "InVivo";
       scatter x = LoadRate y = absorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
       series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80/axis=y transparency =
0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis values = (0 10 20 30 40 50 60 70 80) label = 'Absorption (%)' ;
run;

title1 'Rat - InVitro';
title2 'Combined database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where species = 'RAT' and StudyType = "InVitro";
       scatter x = LoadRate y = logitabsorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
       series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline -8 -6 -4 -2 0 2 4/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis label = 'Logit(Absorption)' ;
run;
title2 'Combined database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where species = 'RAT' and StudyType = "InVitro";
       scatter x = LoadRate y = absorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
       series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
       refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
       refline 10 20 30 40 50 60 70 80 90/axis=y transparency = 0.5;
       xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
       yaxis values = (0 to 90 by 10) label = 'Absorption (%)' ;
run;

title1 'Rat - InVivo';
title2 'Combined database: Observed data & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
       where species = 'RAT' and StudyType = "InVivo";
       scatter x = LoadRate y = logitabsorption;
       styleattrs datacontrastcolors=(black blue red);
       series x = LoadRate y = Pred  / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 1 thickness=2);
```

```
      series x = LoadRate y = lower / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
      series x = LoadRate y = upper / group = ExpDuration SMOOTHCONNECT  lineattrs =
(pattern= 34 thickness=0.1);
      refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
      refline -10 -8 -6 -4 -2 0 2/axis=y transparency = 0.5;
      xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
      yaxis label = 'Logit(Absorption)' ;
run;
title2 'Combined database: Observed Absorption & Predicted curves vs. Loading Rates';
Proc sgplot data = outp ;
      where species = 'RAT' and StudyType = "InVivo";
      scatter x = LoadRate y = absorption;
      styleattrs datacontrastcolors=(black blue red);
      series x = LoadRate y = Pred_absorption  / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 1 thickness=2);
      series x = LoadRate y = lower_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
      series x = LoadRate y = upper_absorption / group = ExpDuration SMOOTHCONNECT
lineattrs = (pattern= 34 thickness=0.1);
      refline 0.01 0.1 1 10 100 1000 10000/axis = x transparency = 0.5;
      refline 0 10 20 30 40 50 60 70 /axis=y transparency = 0.5;
      xaxis type = log logbase=10 logstyle=logexpand values=(0.01 0.1 1 10 100 1000
10000 50000) label='Loading Rate (ug/cm2)';
      yaxis values = (0 to 70 by 10) label = 'Absorption (%)' ;
run;
ods rtf close;
```