ARTICLE

What Can Be Learned From Crowdsourced Population Asparagus Urinary Odor Kinetics?

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Asparagus consumption is associated with the production of malodorous urine. Interindividual variability was previously characterized by an American Society for Clinical Pharmacology and Therapeutics crowdsourced study. To further characterize urinary odor kinetics, we conducted a study with consenting participants from Takeda Pharmaceutical International Company. The participants were randomized to consume a specified number of asparagus spears and asked to record urine odor. A kinetic-pharmacodynamic model characterized the data from both the newly conducted Takeda study ($N = 42$) and the previously analyzed American Society for Clinical Pharmacology and Therapeutics studies (total $N = 139$). The updated model included the identification of an absorption process with a half-life of 25 minutes. We estimated the elimination half-life of the asparagus effect on malodorous urine to be 7.2 hours, which was 44% longer in our study. We built on previous experience using an improved R-Shiny app for conducting the crowdsourcing experiment, further demonstrating the utility of this population kinetics approach in organizational and educational settings.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Perceived urinary odor kinetics interindividual variability after the consumption of asparagus spears were previously characterized by an American Society for Clinical Pharmacology and Therapeutics crowdsourced study. However, there is a continued need to refine the kinetic-pharmacodynamic (K-PD) model, as well as to educate on clinical pharmacology topics across organizational and educational settings.
WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This crowdsourced clinical study (Takeda Translational Research and Early Clinical study) aimed to further characterize asparagus urinary odor perception kinetics and associated variability in healthy participants, as well as to refine the K-PD model.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The refined K-PD model included the identification of an absorption process with a half-life of 25 minutes. We estimated the half-life of the asparagus effect on malodorous urine to be 7.2 hours, which was 44% longer in our study.
HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ The current study further demonstrates the utility of this population kinetics approach in organizational and educational settings.

Takeda Pharmaceutical International Company places great emphasis on raising awareness and providing training and education on clinical trials for its employees as part of its general curriculum on the maintenance of scientific integrity and compliance. Although there is continuous training on pharmacokinetics and various aspects of the design and conduct of clinical trials, we observed a need to educate employees more broadly on the complexities of conducting clinical trials and, more importantly, to provide them with a greater understanding of how all this information comes together. We also recognize that educational aspects are best adopted by introducing fun components to learning.

We were inspired by the recent success of the crowdsourcing asparagus study[1] conducted during the American Society for Clinical Pharmacology and Therapeutics (ASCPT)

Annual Meeting and identified this study as an important tool (model) and opportunity to address both the educational and fun aspects of learning. The published crowdsourcing study also provided an opportunity to reemphasize the "Learn and Confirm" paradigm,[2] which influenced our operational and scientific objectives. Consequently, the lessons learned from the previous study[1] were used to alter selected design and operational aspects of our study. There was a need to redesign the data collection process by developing a web-based application for topics related to the overall management of the study, from randomization to data recording and real-time data exploration. In addition, our scientific "Learn and Confirm" objective was to use the ASCPT study to not only further model refinement but also to allow for a comparison between the two populations and potentially identify

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any new sources of interindividual variability that would enhance our understanding.

To maximize the number of participants, we chose a face-to-face Takeda Translational Research and Early Clinical (TREC) Functional Meeting as the ideal venue to reach out to and engage with all participants as well as provide them with the opportunity to engage in a fun exercise for the operational part of the trial.

The anecdotal health benefits of asparagus are frequently discussed in health and nutritional magazines, although not all evidence points to such benefits.[3] The phenomenon of odorous urine following asparagus ingestion is not familiar to everyone because a fraction of the population do not produce odorous urine and/or cannot smell it. These groups of people differ with respect to the production of asparagus sulfurous metabolites and/or their ability to perceive the odor.[4–6]

To date, there are no reports of specific genes or xenobiotic- metabolizing enzymes involved in the production of asparagus odorous metabolites, despite the fact that there are up to 29 different compounds from asparagus that may be odorous. Although it is difficult to characterize precisely which molecules are malodorous, methanethiol or methyl–mercaptan are the most predominant.[7] In contrast to the metabolizing enzymes potentially involved in the production and disposition of the odorous metabolites, more information has recently become available with respect to the olfactory genes that may be associated with anosmia.[8] Indeed, a recently reported genome-wide associated study involving 6,909 individuals reported that 871 single-nucleotide polymorphisms reached genome-wide significance for asparagus anosmia, highlighting that the ability to smell the metabolites of asparagus consumption varies among people and across populations.[8] Although the sources of variability in the production and perception of asparagus odorous metabolites are scientifically intriguing, they have been discussed in detail elsewhere[4–9] and will therefore not be discussed further here.

To execute the current study within the timeframe of the meeting (and a data collection period of 72 hours postingestion of asparagus), we decided to use the protocol from the original study at the ASCPT meeting[1] but with some minor adaptations. The greatest operational difference from the ASCPT study was the development of the electronic case report form (eCRF) and the study management system that was implemented as an R-Shiny app, which was installed on an Amazon cloud web server and made available to the study participants on smart phones and computers via the internet. Since the entire study was performed on the eCRF R-Shiny app, operationally we could execute the study, collect data, and address any queries efficiently.

METHODS
Study conduct
The TREC Asparagus-001 Study (TREC study) was an open-label, randomized study designed to evaluate the ability of healthy volunteers (participants) to detect the sulfurous odor associated with urinary metabolites of asparagus. Up to 100 volunteers were planned to be enrolled and randomized to receive 0, 3, 6, or 9 spears of broiled asparagus in a 1:2:2:2 ratio. The study was conducted on November 30, 2017. Approval was granted by the Quorum Review Institutional Review Board (Seattle, WA). The final notice of approval is included in **Supplementary Material S1**.

Since this was a crowdsourced study with limited resources, we implemented a web-based application using R-Shiny to support automated study procedures, including informed consent, screening, randomization, and data collection. The app was further used for the management of study tasks, such as study population management, tracking of informed consent, real-time data collection, and visualization of results. The chronology and conduct of the study, together with detailed instructions, were added as a bespoke functionality to the R-Shiny app and provided clear guidance on the conduct of the trial. The app was installed on a customized Amazon (Seattle, WA) Elastic Compute Cloud (AWS EC2) and thus could be used by all participants without prior local software installation.

The primary objective of this study was to investigate if and for how long participants could detect the smell of asparagus metabolites in urine postconsumption. Secondary objectives were to assess the time course of the perception of asparagus odor in urine postconsumption and the dose–response relationship between the amount of asparagus consumed and the duration of detection of asparagus odor in the urine.

The main inclusion criteria were the following: (i) male or female participants older than 21 years of age, (ii) attendance at the TREC meeting in person on November 30, 2017, (iii) informed of the nature and risks of the study, and (iv) provision of written informed consent prior to screening.

The main exclusion criteria were the following: (i) history of allergy to or dislike/intolerance for asparagus, (ii) participation in another study that contraindicated the participant from eating asparagus, (iii) prior consumption of asparagus 24 hours before the start of the study, (iv) any other condition or prior therapy that, in the investigator's opinion, would make the participant unsuitable for the study or unable or unwilling to comply with the study procedures, and (v) unwilling or unlikely to comply with the requirements of the study. All criteria were based on answers to prespecified questions that were asked by the app. After all questions were answered by a given participant, the app checked the inclusion and exclusion criteria that were built into the R-Shiny app, which in turn allowed automatic randomization or the exclusion of participants from the study.

During the screening phase, the participants were asked to self-report their demographic data, conditions (suitability for study), treatment, and observations into a web-based eCRF. The participants were also exposed to two control samples (water and a commercially available perfume) to evaluate their olfactory perception. The participants who did not pass the screening procedure because of data entry errors could correct their screening information.

The participants who passed the screening process were randomized into the study and were requested to enter the

date and time of treatment and the number of asparagus spears consumed. In addition, observations on urine odor were requested to be self-reported at any time (pretreatment or posttreatment). The observation period ended 72 hours posttreatment or after two consecutive odor records with "no odor." Odor records consisted of the date and time of the observation and an odor score consisting of seven levels ranging from 0 = "no odor" to 6 = "intolerable or offensive odor." In addition, an option of "forgot to smell" was available. The details of the R-Shiny app code are available in **Supplemental Materials S2**.

On the day of the meeting, potential participants were educated on the study design, the requirements for participation in the study, and the use of the R-Shiny app. The principal investigator and the operational team were present throughout the day on site to respond to any questions or issues that occurred during the clinical phase. Once all of the participants were fully informed about the study and had signed the consent form, they were provided with a username and password via e-mail that enabled them to log in to the app.

Model-based analysis

As a starting point for data analysis, the previously developed ASCPT model was used.[1] This model aimed to characterize the relationship between the number of asparagus spears consumed and the observed odor scores over time. For this purpose, a latent (unobserved) asparagus exposure over time ($A(t)$) was used, which was assumed to follow a one-compartment linear pharmacokinetic model. The odor score (pharmacodynamics) was then modeled as a multinomial logistic regression with $A(t)$ as a dependent variable. Since $A(t)$ was not observed, the model can be described as a kinetic-pharmacodynamic model.[1]

The relationship between the number of asparagus spears consumed ($Dose_i$) for individual i and the (latent) asparagus exposure was characterized using an exposure half-life ($t_{1/2}$) as follows:

$$A_i(t) = Dose_i \cdot e^{\frac{\ln(2)}{t_{1/2,i}} \cdot t} \qquad (1)$$

We used the subscript i to indicate individual parameters. If $y_{i,n}$ represents the observed score for individual i at time t_n, then the probability to observe a score with intensity j or above ($j = 1,\ldots$) was defined using an inverse logistic transformation as follows:

$$P(y_{i,n} \geq j) = \frac{e^{f_{i,n,j}}}{1 + e^{f_{i,n,j}}} \qquad (2)$$

where $f_{i,n,j}$ is defined as the sum of the first j baseline coefficients β_k and the asparagus concentration effect at time t_n:

$$f_{i,n,j} = slope_i \cdot A_i(t_n) + \beta_{1,i} + \sum_{k=2}^{j} \beta_k \qquad (3)$$

It should be noted that $\beta_{1,i}$ was estimated as an individual parameter (i.e., with a random effect), which is why the subscript i was used here: $\beta_{1,i} - N(\beta_1, \omega_\beta)$. All other baseline coefficients β_k with $k \geq 2$ were only estimated on a population level.

Furthermore, it should be noted that $P(y_{i,n} = 0)$ was defined as $1 - P(y_{i,n} \geq 1)$ to ensure that all probabilities sum up to 1.

In the previous equation, $slope_i$ is the individual exposure–response slope parameter (with a random effect) relating the (unobserved) asparagus exposure time course $A_i(t)$ to the observed odor scores $y_{i,n}$ at times t_n. There was a covariate effect of age on slope resulting in the following parameter model:

$$slope_i \sim \text{LN}(slope_{pop} \cdot age_i^{slope_{age}}, \omega_{slope}) \qquad (4)$$

Since the baseline coefficients β_k were estimated on a logistic scale, the random effect on β_1 was modeled according to an additive relationship following a normal distribution. The random effect on *slope* was modeled according to an exponential relationship following a log normal distribution. Both random effects were modeled independently, that is, without a covariance term. **Figure 1** shows the model structure as a diagram.
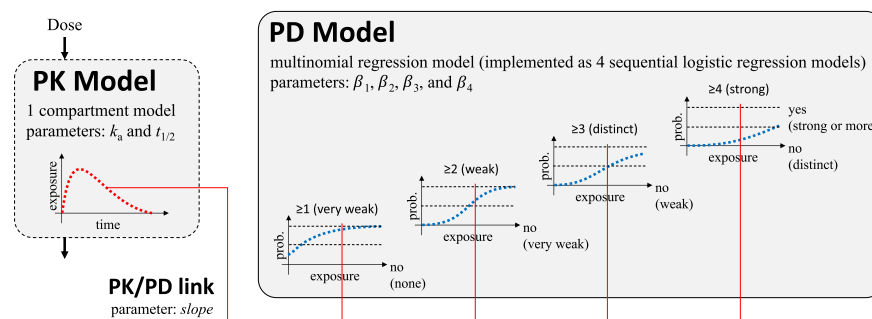

Figure 1 Model structure of the K-PD model for asparagus odor scores. The left box represents the (P)K model, which is a one-compartment linear model with two parameters, an absorption rate constant (k_a), and an elimination half-life ($t_{1/2}$) that describes the (unobserved) exposure as a function of dose (asparagus exposure) and time (red dotted line). The right box represents the PD model, a multinomial regression model to characterize the probability of odor scores to be "none," "very weak," "weak," "distinct," or "strong or more." This model consists of four sequential ordinary logistic regression models ($j = 1,2,3,4$), each describing the probability $P(y_{i,n} \geq j)$ (blue dotted lines). The predicted asparagus exposure (red solid line) was scaled by the sensitivity parameter slope and used as an input to the multinomial regression PD model. K-PD, kinetic-pharmacodynamic, PK, pharmacokinetics; PD, pharmacodynamics, prob, probability.
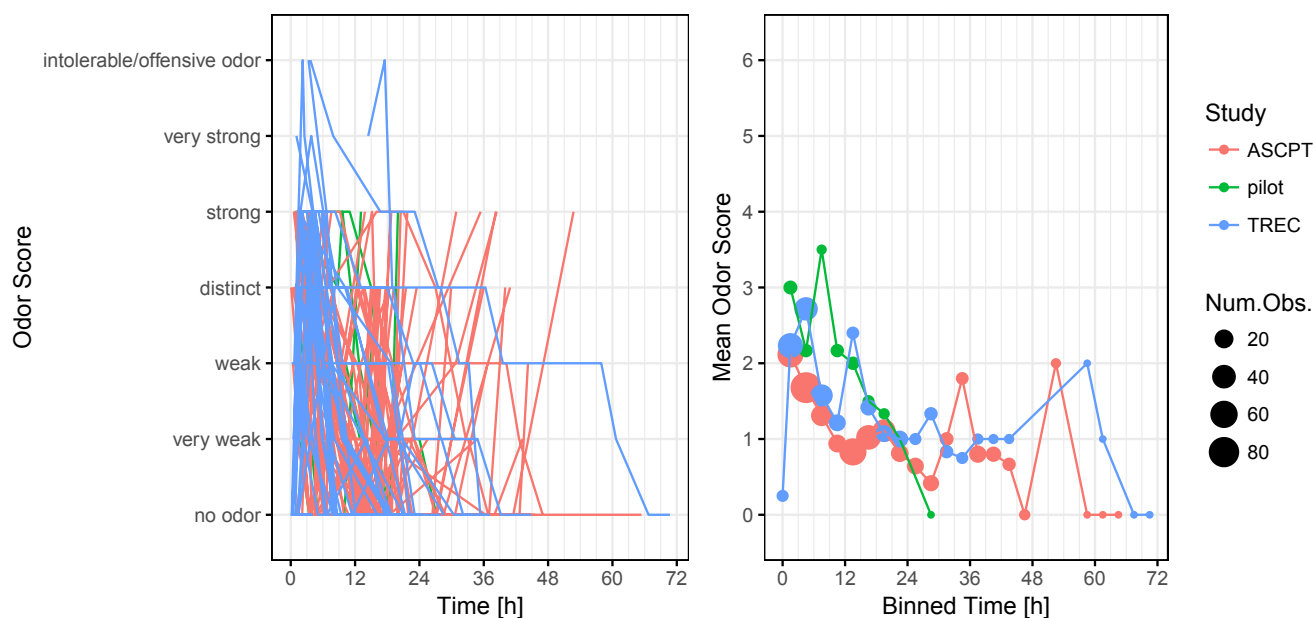
Figure 2 Raw (left) and mean (right) odor scores over time grouped by study. Times were binned into 3-hour intervals for the right panel. The left panel shows the raw odor scores over time as a spaghetti plot. Scores of grade 4 (strong) and higher were merged into category "strong+" for the subsequent analysis. The right panel shows mean odor scores in 3-hour intervals over time. Point sizes indicate the number of observations averaged per time interval. ASCPT, American Society for Clinical Pharmacology and Therapeutics; h, hour; TREC, Translational Research and Early Clinical.

Model development was conducted using NONMEM version 7.4.1.[10] The LAPLACE estimation method was used for parameter estimation. All data management and visualization were performed in R version 3.3[11] using primarily Shiny, ggplot2, and several tidyverse packages.

RESULTS
Data
All collected data were merged in real time into a study database for subsequent analysis by the R-Shiny app. In addition, the data file used in the ASCPT publication was merged with the TREC study data. This combined dataset was used for real-time visualization of the collected results, as well as for the subsequent model-based analysis described later (**Supplementary Material S3**).

In total, 48 participants signed the informed consent form for the TREC study. Of these, 45 participants passed the screening requirements and were randomized into the study. Overall, 43 participants were treated with their assigned number of asparagus spears, with 42 participants having at least one valid observation. The number of recorded odor observations in the TREC study is shown in **Table S1**. Due to of the fact that there were only nine observations with a score of 5 and above, we combined odor scores 4–6 in alignment with the ASCPT dataset.

The combined dataset comprised observations from 139 participants in total: 42 from the TREC study, 80 from the ASCPT main study, and 7 from the ASCPT pilot study. The latter two studies were grouped into "ASCPT+" for the analysis described here. The planned and actual number of asparagus spears in the combined dataset is provided in **Table S2**. The demographics of participants

included in the combined dataset are summarized in **Table S3**.

Exploratory analysis
Figure 2 shows the raw odor scores over time (left panel) and summarizes odor scores over time by showing mean odor scores in 3-hour intervals grouped by study (right panel). The number of summarized records was illustrated by the point size. There were several participants in the ASCPT study with increasing odor scores toward the end of the observation period. The TREC study dataset comprised a number of predose and early postdose observations revealing an initial increase in the mean odor scores. Therefore, we tested the model to characterize an absorption phase in the model-based analysis. In addition, we found higher odor scores after 36 hours and a prolonged duration of odor records in the TREC study when compared with the ASCPT studies. We tested for a potential study dependent odor half-life.

As a first analysis step, we simulated the TREC study using the model that was previously developed on the ASCPT data and compared these simulations with the actually observed data (see **Figure 3** for this cross-visual predictive check). Overall, the model adequately predicted the TREC study data with the exception being the lower odor scores, most prominently at the early/predose and late observations of "no odor" records.

Model-based analysis
From the cross-visual predictive check, it appeared that the largest deviation between observation and simulations was at early time points. As a consequence, we tried
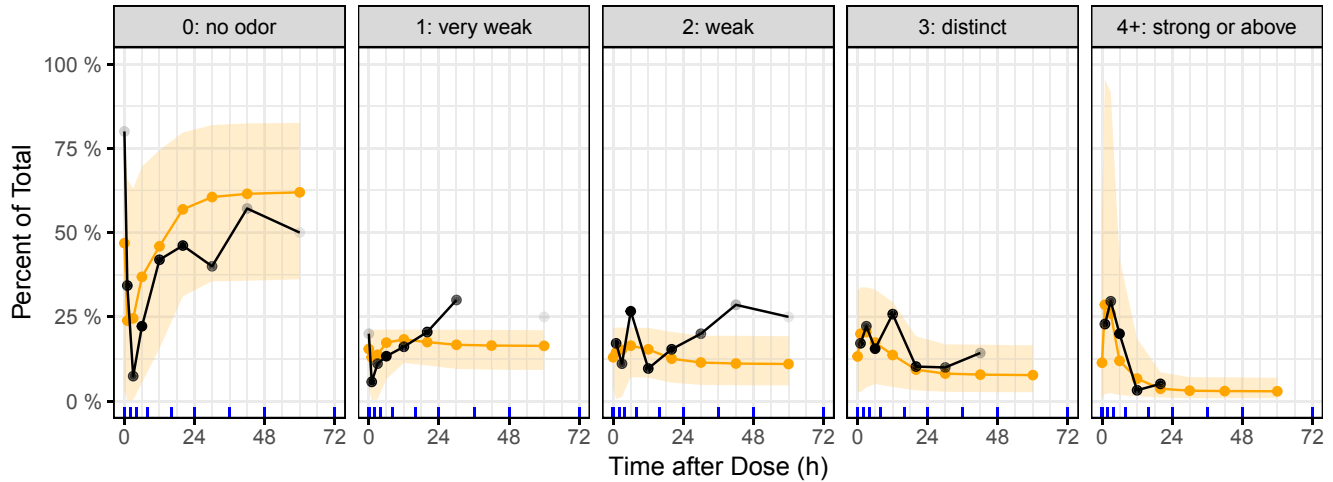
Figure 3 Overlay of simulations performed with the ASCPT model and observations from the TREC study. This cross-visual predictive check illustrates the percentage of odor scores over time. Odor score probabilities were simulated for scores 0, 1, 2, 3, and 4+ (4 or higher) over time and summarized as mean and 90% prediction intervals (illustrated as orange line and shaded band in the figure). These simulations were overlaid with frequencies of observed odor scores in the TREC study (black dots). Transparency was used to indicate the number of observations summarized. The blue ticks at the bottom of each panel indicate time bin intervals used to summarize simulations and observations. ASCPT, American Society for Clinical Pharmacology and Therapeutics; h, hour; TREC, Translational Research and Early Clinical.

to improve the model by adding an asparagus absorption process.

The ASCPT model described the (latent) asparagus exposure as a first-order elimination (see Eq. 1). Since the TREC study dataset contained predose observations and observations shortly after asparagus consumption, we could characterize an absorption process as well. We used a first-order linear absorption process; that is, we modified Eq. 1 and modeled the asparagus exposure time course as the following:

$$A_i(t) = \frac{k_a}{k_a - k_e} \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) \qquad (5)$$

with $k_e = \ln(2)/t_{1/2}$.

Since the parameter estimates were similar between the ASCPT model and the adopted TREC study model, we applied the new model with k_a to the combined dataset. Model diagnostics indicated that individual estimates for the *slope* parameter were different by study.

Frequently, dose–response sensitivity parameters, such as *slope* are assumed not to be different across studies. Therefore, we tested two models to characterize this observed difference: one with a study-specific slope parameter and the other with a study-specific half-life. The latter model was based on the hypothesis that a different half-life would cause a different (unobserved) asparagus exposure, which in turn would explain the apparent difference in the exposure–effect slope.

Both models did fit the data substantially better with an almost equal drop in the objective function value (−6.59 and −7.11, respectively). As a consequence, we extended the model to estimate a study specific half-life parameter.

The resulting model was our final model. Parameter estimates are listed in **Table 1**. Asparagus was quickly absorbed, with the typical absorption half-life (natural logarithm (2)/ka)

Table 1 Final parameter estimates of the final model

Type	Parameter	Estimate	95% CI
Fixed effect	$\ln(k_a)$	0.5144	(−0.006373 to 1.035)
	$\ln(t_{1/2})$	1.3700	(1.007 to 1.733)
	TREC on $t_{1/2}$	44.1700	(0.7245 to 87.61)
	slope	−0.6233	(−0.9998 to −0.2468)
	Age on *slope*	−1.9320	(−3.72 to −0.1449)
	β_1	−0.6498	(−1.029 to −0.2711)
	β_2	−0.8881	(−1.082 to −0.6942)
	β_3	−0.9981	(−1.188 to −0.8082)
	β_4	−1.4980	(−1.847 to −1.149)
Random effect	BSV slope	0.3918	(0.1085 to 0.675)
	BSV β_1	0.4378	(0.007365 to 0.8683)

β_1, β_2, β_3, β_4, beta-1, beta-2, beta-3, beta-4, baseline coefficients of the multinominal regression; BSV, between-subject variability; CI, confidence interval; ka, absorption rate constant; $t_{1/2}$, elimination half-life, TREC, Translational Research and Early Clinical.

estimated at 25 minutes. However, elimination was much slower, with a typical elimination half-life of 3.9 hours for participants in the ASCPT studies and 44% slower (7.2 hours) in the TREC study.

Figure 4 shows a visual predictive check of the final model stratified by study. Both the early and late observations were clearly matched better in the final model when compared with the original ASCPT model (see comparison with **Figure 3**). Overall, the model adequately fitted both studies (during model development, we identified both the ASCPT main study and ASCPT pilot study as ASCPT+) at all times and across all odor scores.

Figure 5 illustrates the distribution of odor score grades over time. The percentage of odor records noting "no odor"
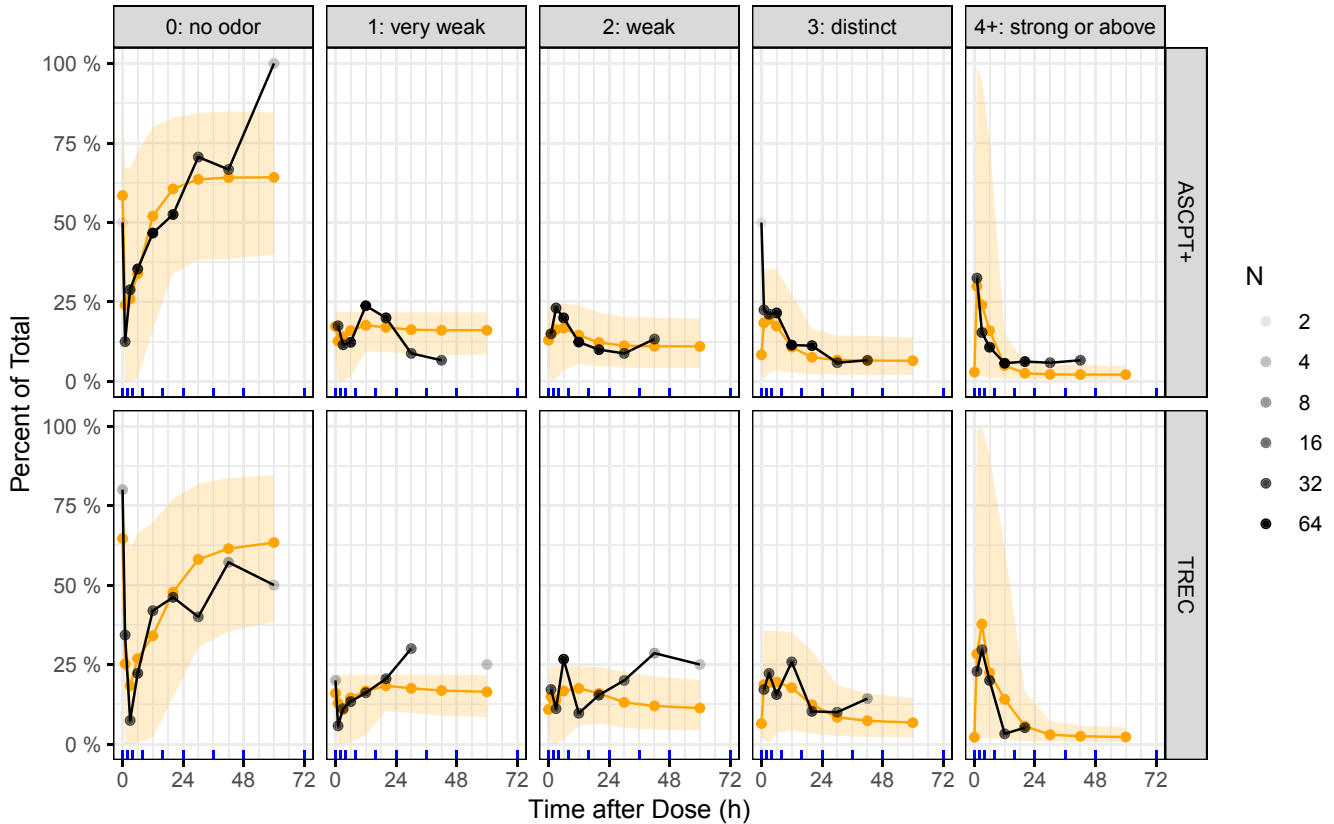
Figure 4 Visual predictive check of the final model. This cross-visual predictive check illustrates the percentage of odor scores over time. Odor score probabilities were simulated for scores 0, 1, 2, 3, and 4+ (4 or higher) over time and summarized as mean and 90% prediction intervals (illustrated as orange line and shaded band in the figure). These simulations were overlaid with frequencies of observed odor scores in the TREC study (black dots). Transparency was used to indicate the number of observations summarized. The blue ticks at the bottom of each panel indicate time bin intervals used to summarize simulations and observations. ASCPT, American Society for Clinical Pharmacology and Therapeutics; ASCPT+, ASCPT main study and the ASCPT pilot study; h, hour; TREC, Translational Research and Early Clinical.
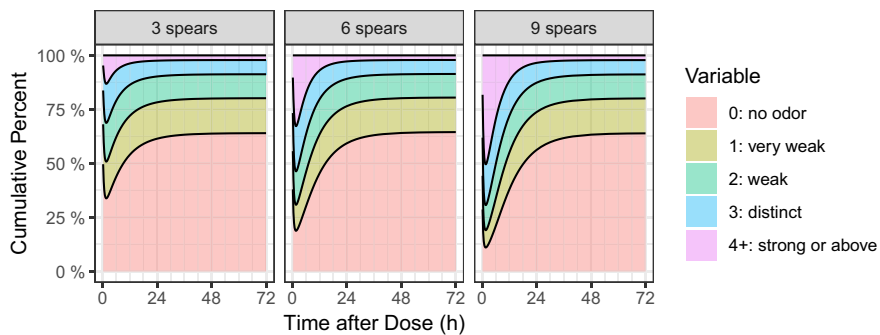
Figure 5 Distribution of odor scores over time, stratified by dose. Shaded areas indicate the percentage of odor scores over time. Areas are staggered on top of each other, summing up to a total odor score percentage (any grade) of 100%. h, hour.

quickly decreased after asparagus consumption with a minimum at approximately 3 hours. With decreasing asparagus exposure, the percentage of "no odor" records increased again toward the end of the observation period at 72 hours. Overall, the percentage of "no odor" scores decreased with increasing dose. On the other hand, the "strong or above" odor records increased over time to a dose-dependent

maximum at approximately 3 hours postdose and decreased again thereafter.

The final model was simulated to illustrate all covariate effects, as well as the dose response of the (unobserved) asparagus exposure and odor score time curves (**Figure 6**). Simulations were performed by age (30, 45, and 60 years), study (TREC and ASCPT+), and dose (3, 6, and 9 asparagus
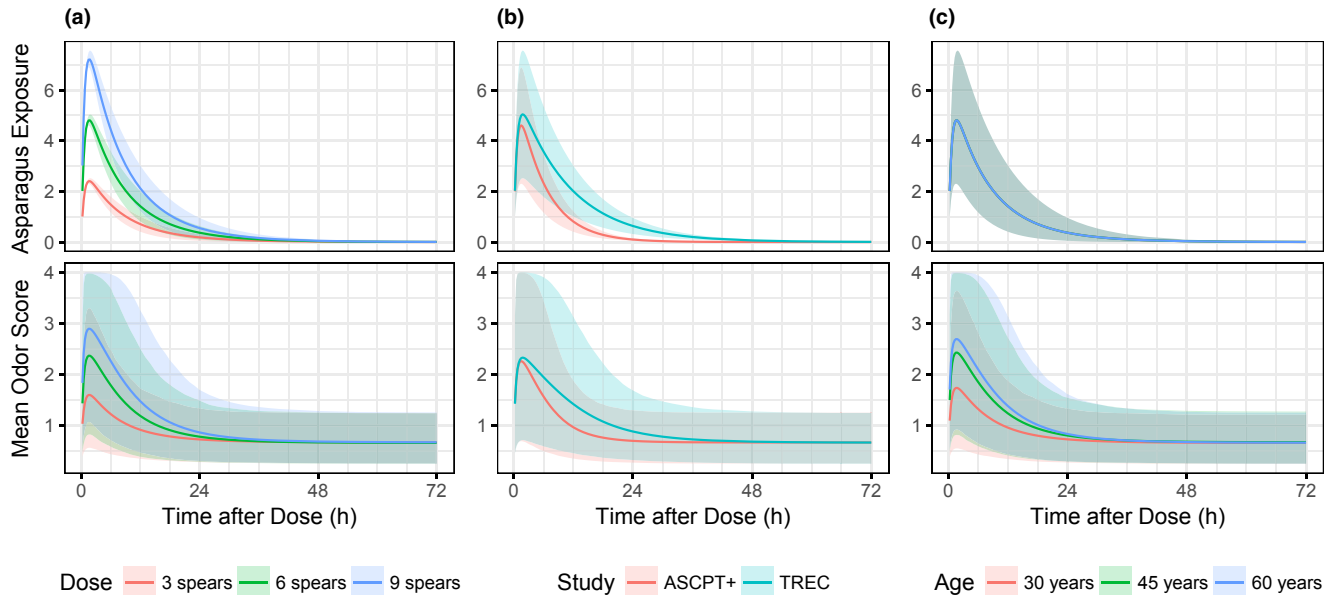
Figure 6 Simulated asparagus exposure (upper row) and mean odor score (lower row) by dose (**a**), study (**b**), and age (**c**) using the final model. Model readouts asparagus exposure and mean odor score were simulated with uncertainty for participants treated with 3, 6, or 9 asparagus spears; in studies ASCPT+ or TREC; and for ages 30, 45, or 60 years. Simulations were summarized and stratified by dose, study, and age. Each panel shows the mean (line) and 90% prediction interval (shaded area) colored by the respective strata. ASCPT, American Society for Clinical Pharmacology and Therapeutics; ASCPT+, the ASCPT main study and the ASCPT pilot study; Asp, asparagus; h, hour; TREC, Translational Research and Early Clinical.

spears). The NONMEM final model and the final model output are included in **Supplementary Material S4**.

DISCUSSION

Our organizational objective was to conduct a crowdsourced study for educational value to expose participants to all aspects of designing, conducting/participating, collecting/analyzing, and reporting outcomes of a clinical study. We also wanted to demonstrate that the application of eCRF platforms in mobile applications (R-Shiny app) can provide a fast, convenient, and reproducible way to conduct, collect, analyze, and report data from clinical studies in real time.

In addition to our organizational objective, we also achieved an unanticipated scientific finding by identifying absorption as an additional pharmacokinetic parameter with tangible physiological effect. From a scientific perspective, we successfully developed a kinetic-pharmacodynamic model to characterize data from both the newly conducted TREC study and the previously analyzed ASCPT studies. Our final model was an extension of the previously developed ASCPT model, with the following two major updates: (i) identification of an absorption process to further characterize the (unobserved) asparagus exposure and (ii) estimation of a different half-life for participants in the TREC study. The exposure half-life was predicted to be 44% longer in the TREC study when compared with the ASCPT studies. The absorption half-life was approximately 25 minutes, indicating a short time frame between the consumption of asparagus and the detection of odor in the urine. The new model adequately predicted odor score levels up to grade 4 (strong) in both the TREC study as well as the ASCPT studies. Consistent with the findings from

the ASCPT study, our study demonstrated that the number of asparagus spears consumed related very well with the strength of odor, as depicted in **Figure 5**. The longer half-life of the odor observed in our study is likely the result of the timing of the study. The TREC study was conducted at lunch time, whereas the ASCPT study was performed later in the day. We speculate that in addition to the timing of the study, a thorough overview of the study objectives and operational procedures and greater compliance in recording of odor scores may have also contributed to the quality of the data collected. Although findings from the ASCPT study were consistent with the assumption that renal function decreases with age, we were more limited in demographic spread to allow for further evaluation on any potential differences in intrinsic and extrinsic factors that may have influenced the half-life.

We recorded only one participant who did not perceive odorous urine after consuming asparagus, a finding in contrast with that observed in previous studies.[1,4,9] Furthermore, when compared with the ASCPT study, our study was more restricted in terms of age range, thereby limiting the opportunity to explore the complete effect of age on renal excretion.

From an operational perspective, although we were fortunate that the ASCPT study team shared their previous experience with us, we still invested a significant amount of time in building the multifunctional Shiny app that included all the necessary domains required for the successful execution of the study and automatic data collection. However, we still faced some challenges with respect to data cleaning, which were raised by email and resolved. Nevertheless, the multifunctional app proved to be a worthwhile investment in terms of both time and effort as it was efficient and removed

a substantial burden from the trial team enabling them to execute the study within 1 day. We also observed a very high compliance rate in our study with only two missing observations. We speculate that there were several reasons for this, namely curiosity, social aspects, raised awareness around the crowdsourcing study, and finally the functionality of the mobile Shiny app. We also observed that anecdotes around asparagus consumption and its potential health benefits further stimulated interaction and discussion. Notably, all participants were invited to a presentation of the final study results. We observed that they were all very curious to see these results and actively engaged in discussions around the study findings following completion of the analysis. Overall, this entire exercise generated a very positive and collaborative atmosphere.

Finally, because we were inspired by the ASCPT study, we wanted to share our experiences and pass the baton onto the community so that others may also attempt this exercise in their organizations or educational institutions. The sharing of such experiences is a strong generator of hypotheses, concepts, and ideas that may add additional value from an educational standpoint and in the long run may further impact the way digital tools are used by researchers in a fast and reliable way. As we pass on this knowledge to the next study cohort, we would also like to share not only our experience and learning, but also the R-Shiny app code that was used to create the app, in the hope that this will be used and further improved in the future.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Table S1. Number of recorded odor observations.
Table S2. Planned and actual number of asparagus spears in the combined dataset.
Table S3. The characteristics of participants in the combined dataset.
Supplementary Material S1. Approval from the Quorum Review Institutional Review Board.
Supplementary Material S2. Zip-archive of R-Shiny app.
Supplementary Material S3. Final analysis dataset.
Supplementary Material S4. Final model as NONMEM control stream and final model output.

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