Systematic Review and Meta-Analysis of Isoniazid Pharmacokinetics Among Healthy Volunteers and Patients with Tuberculosis

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ABSTRACT

Purpose: To derive and compare isoniazid (INH) pharmacokinetic (PK) summary estimates between healthy volunteers and TB patients, evaluate whether the current INH dose regimen is appropriate in TB patients, and evaluate the impact of N-acetyl-transferase-2 (NAT2) status on INH PK.

Methods: A systematic approach was conducted to find studies with relevant INH PK data published in the English language up to February 2018. INH PK parameters were extracted with their respective INH dosages and were dose-normalized to allow a fair comparison between healthy volunteers and TB patients. Meta-analysis was then performed for the C_{max} and AUC estimates for all INH dosages

Findings: Ninety studies were included in this systematic review. TB status significantly affected the INH C_{max} and AUC estimates. In adult healthy volunteers, the dose-normalized INH C_{max} and AUC were statistically higher than TB patients. There were no significant differences in dose-normalized C_{max} and AUC between TB and TB/HIV patients in adults; however, pediatric AUC was significantly different between TB and TB/HIV patients. Additionally, no significance was observed comparing the dose-normalized C_{max} and AUC of pediatric TB and TB/HIV patients to their respective adult counterparts. Dose-normalized INH C_{max} and AUC in fast and intermediate NAT2 patients were significantly lower than slow NAT2 patients.

Implications: The current recommended dosages of INH were found to produce less drug exposure in TB patients when compared to healthy volunteers. NAT2 polymorphism greatly impacts INH PK, hence testing for acetylator status is highly recommended and therapeutic drug monitoring would help reduce INH toxicity.

Keywords: Isoniazid; Pharmacokinetics; Meta-analysis; Systemic Review; TB patients

Introduction

Isoniazid (INH) has been a key drug for treating drug-susceptible TB for decades. When combined with other first-line medications, including rifampicin (RIF), ethambutol (EMB), and pyrazinamide (PZA), treatment duration is manageable and usually effective. As of 2017, there were 558,000 TB drug-resistant cases estimated worldwide—where 82% of these cases were considered MDR-TB showing resistance to both INH and rifampicin [1]. As a result, the need for an adequate TB treatment is imperative.

Despite the wide use of INH, the optimal dose to treat TB has not been established. The drug was discovered in 1952, thereafter INH has been combined with other anti-tuberculosis agents to combat TB and drug resistance [2]. However, differences in PK between healthy volunteers and TB or TB/HIV coinfected patients are not well-known. Patients with diabetes, HIV, and other gastrointestinal problems are at risk for poor drug absorption. Further, drug-food or drug-drug interactions also might affect INH absorption, and in turn may lead to poor treatment outcomes.

In terms of therapeutic drug monitoring (TDM), AUC is an indicator of clinical outcomes in TB patients, in which an AUC of ≤ 52 mg·hr/L was shown to be associated with a poor outcome [3]. An INH C_{max} of 3-6 mg/L from daily INH 300 mg dose and 9-15 mg/L from 900 mg bi-weekly dose is desirable; however, plasma concentrations alone cannot guarantee TB treatment outcome [4].

INH absorption is greatly hindered by the presence of food in the stomach [5], and it is extensively metabolized by the liver where it undergoes phase II conjugation via N-acetyltransferase-2 (NAT2). Studies have shown NAT2 polymorphism affects the plasma concentrations of INH [6-8]. Adult patients who are fast acetylators may have suboptimal exposures with the current INH dose of 5 mg/kg [9]. Patients with slow NAT2 may display higher AUCs and thus may have significantly greater bactericidal activity than intermediate and fast NAT2 patients [10]. Therefore, the relationship between NAT2 and INH PK

requires further examination. In terms of safety, the risk of hepatotoxicity may be increased in patients who are slow metabolizers [11-14].

The currently available INH PK data in literature are from relatively small cohorts and more robust data is needed. Additionally, there are inconsistencies in INH concentrations for TB patients. For these reasons, a systematic review and meta-analysis was conducted in order to obtain and summarize INH C_{max} and AUC data. The objectives of this study were: (i) to derive and compare INH PK summary estimates between healthy volunteers and TB patients; (ii) to evaluate whether the current INH dose regimen is appropriate in TB adult and pediatric patients; and (iii) to evaluate the effect of NAT2 status on INH C_{max} and AUC.

Methods

Search Strategy and Selection Criteria

A systematic literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. The electronic databases used were: PubMed, EMBASE, and Scopus. Studies were identified using the search terms: ((INH OR isoniazid OR antimycobacterial) AND pharmacokinetics AND antituberculosis). The search was conducted for the period from the earliest study in 1966 to February 2018 in English. R. D. and B. L. H. assessed titles and abstracts for relevance and reviewed full texts for inclusion with regards to the selection criteria. Studies were included if they reported INH PK data from healthy adult volunteers or from patients with TB. Patients who received INH for indications other than TB, specifically other mycobacterial infections, were excluded. In vitro studies, studies without INH C_{max} and AUC, and studies that assessed PK under fed-state (when indicated), were excluded. Furthermore, reviews or systematic reviews of INH PK were also excluded to avoid potential data duplications.

Quality of Studies Assessment

There are no validated tools to evaluate PK studies. However, our priority was to obtain studies that represented the target population which received INH and reported relevant PK parameters. All INH dose ranges were considered in this analysis. In order to enhance the data extraction process, we only included the articles in which authors precisely described their study sample, pharmaceutical product, method, and statistical tools for analysis.

Data Extraction

A standardized extraction form was developed by R. D. and was later modified by B. L. H. Two reviewers (P. L. and B. L. H.) extracted data from the included studies. The parameters of interest included study population and size, age (adult ≥ 18 years old, pediatric < 18 years old), gender, body weight, INH C_{max} and AUC, formulation and route, treatment frequency and duration, NAT2 status, TB status, HIV status, smoking status, malnourishment, and analytical method. In addition, subjects in studies must be in a fasting-state prior to taking INH.

Data Synthesis

In many studies, multiple groups of subjects were compared [16]. In others, crossover studies were performed in order to compare different INH formulations [17]. These groups were handled as separate study arms as presented in the study; each contributed their own set of INH PK data towards the summary estimates instead of a composite mean value for each study. Therefore, some studies contributed more than one set of PK parameters towards this meta-analysis. The forest plots were handled using the same process. Subjects in studies without any reported INH PK data were excluded, as a result, only subjects with INH PK data were included in this meta-analysis. To enable a comparison between all studies, sample size, data means and standard deviations (SD) were collected for the meta-analysis.

When studies did not include body weight of adult subjects, we used the world average body weight of 62-kg to calculate body-weight dosing (mg/kg) [18]. Body-weight dosing was used to dose-normalize INH PK data for a fair comparison across all doses. Additionally, the majority of healthy adult volunteers only took INH; whereas TB patients commonly took INH in combination with other anti-tuberculosis medications (i.e. RIF, EMB, and PZA). Therefore, subjects were included if they took INH alone or in combination with other antituberculosis medications. Any subjects taking INH with other co-medications were also included if the study concluded that the co-medications did not significantly impact INH PK.

The majority of INH studies have reported C_{max} and AUC data in mean±SD, but there were others that only reported the mean or median and omitted standard deviation. This was especially true in the earlier INH studies; therefore, we formulated various assumptions and methods to estimate and reconcile the differences in these study data. If raw data were available in studies, we used that to calculate the mean and standard deviation for those studies. If the AUC was not explicitly stated in the study while raw data were available, we performed non-compartmental analysis (NCA) on the plasma concentrations over time (four blood-sample collection time minimal) to estimate the AUC. The AUC of studies were excluded if the duration of sample collection was less than six hours, since the full drug-plasma level is difficult to estimate accurately with less than three half-lives of collection (less than six hours). Since studies reported a mixture of single-dose and steady-state AUC, along with different AUC range (i.e. $AUC_{0\text{-}6h}$, $AUC_{0\text{-}8h}$, $AUC_{0\text{-}12h}$, etc.) in tables, this would make it difficult to compare and summarize the data for the analysis. Subsequently, $AUC_{0\text{-}6h}$ or greater was considered as representing AUC and the combination of single-dose and steady-state AUC were combined in this analysis. If data were given in median, range, or IQR, these were standardized to mean and standard deviation via the described method [19].

Summary Measures

The data were gathered on a standard extraction form. The focus of this study was to collect INH C_{max} and AUC across various doses from all subjects who received INH. A linear model was used to include these variables: healthy adult vs TB adult/pediatric patients, HIV status, and NAT2 status (fast, intermediate, or slow). Data were dose-normalized to prepare for entry and were analyzed by Open Meta-Analyst (http://www.cebm.brown.edu/openmeta/) software using the random-effects/DerSimonian-Lard method to generate forest-plots and summary mean estimates of INH C_{max} and AUC, and calculate heterogeneity (I^2) [20]. Finally, the p-value was obtained using unpaired, two-tailed Student's t-tests performed in Excel, in which 0.05 or less were considered statistically significant. The degree to which INH dose impacted C_{max} and AUC was assessed using meta-regression by Open Meta-Analyst.

Results

The systematic literature search retrieved 4,911 studies, of which 90 studies met the INH inclusion criteria (Figure 1) and a brief summary of these studies is outlined in Table S1 (available as Supplementary Data). The health, age, and NAT2 status of study participants, and the number of PK sets contributed by participants are presented in Table 1-3. The majority of studies used HPLC to measure INH concentrations. The results for C_{max} and AUC presented henceforth include all dose ranges of INH reported in the studies. Unless explicitly stated, any C_{max} and AUC mentioned hereafter will refer to the dose-normalized C_{max} and AUC measures.

TB status significantly affected the C_{max} and AUC estimates of INH. In healthy volunteers, the dose-normalized INH C_{max} and AUC were statistically higher than TB adult, with $P < 0.0001$ for C_{max} and $P = 0.0006$ for AUC (Table 1 and Table 2). The same results were seen when comparing healthy adult volunteers to TB pediatric patients ($P < 0.0001$ and $P = 0.0002$ for C_{max} and AUC, respectively). The same trends were also observed for dose-normalized C_{max} and AUC when comparing healthy adult volunteers to TB/HIV adult and pediatric patients. Dose-normalized C_{max} and AUC for healthy adult volunteers were

1.089 (mg/L)/(mg/kg) [95% CI, 0.969-1.209] and 4.329 (mg·hr/L)/(mg/kg) [95% CI, 3.818-4.840], respectively; whereas adult dose-normalized C_{max} and AUC for TB patient were 0.698(mg/L)/(mg/kg) [95% CI, 0.637-0.759] and 3.183 (mg·hr/L)/(mg/kg) [95% CI, 2.804-3.563], respectively. Similarly, dose-normalized C_{max} and AUC for pediatric TB patient were 0.618 (mg/L)/(mg/kg) [95% CI 0.517-0.718] and 2.695 (mg·hr/L)/(mg/kg) [95% CI, 2.315-3.075]. The dose-normalized AUC forest plots of INH are shown in Figure S1 (available as Supplementary Data) and Figures 2-4. Despite dose-normalization for C_{max} and AUC, pooled statistics demonstrated that high heterogeneity was present throughout this meta-analysis (I^2 > 88%, with the only exception being INH AUC for pediatric TB/HIV, I^2 ~ 60%, demonstrating moderate heterogeneity).

Dose-normalized C_{max} and AUC for pediatric TB only were not statistically significant when compared to their adult TB counterparts ($P = 0.18$ and $P = 0.16$, respectively). There was also no difference perceived for pediatrics with TB/HIV and adults with TB/HIV when their C_{max} and AUC (P = 0.11 and P = 0.22) measures were compared. However, there was a significant difference in AUC between pediatric TB patients and pediatric TB/HIV patients ($P = 0.007$); this difference was not seen in C_{max} for these two groups ($P = 0.34$).

Polymorphism of NAT2 impacted dose-normalized INH C_{max} and AUC. The effect was most apparent between slow NAT2 and intermediate/fast NAT2 subjects (Table 3). The dose-normalized C_{max} was significantly lower for intermediate ($P = 0.017$) and fast ($P < 0.0001$) NAT2 acetylators compared to slow NAT2 acetylators. Likewise, the AUC was significantly lower for intermediate ($P < 0.0001$) and fast ($P < 0.0001$) NAT2 acetylators than slow NAT2 acetylators.

The C_{max} and AUC appeared to increase proportionally to INH dosage. Meta-regression shows a linear relationship between INH body-weight dosing and C_{max} and AUC (Figure 5).

Discussion

The dose-normalized summary estimates of C_{max} from TB population is significantly lower than that of healthy volunteers (36% lower in TB adults, 39% lower in TB/HIV adults, 43% lower in TB pediatrics, and 54% lower in TB/HIV pediatrics). This result of TB/HIV adult patients support what was observed in another study where C_{max} of TB/HIV adult patients had INH concentrations below the reference range of 3-6 mg/L (54/77 patients at week-2, 38/59 patients at week-8, and 15/24 patients at week-24 were below the reference range) [21]. Likewise, the dose-normalized INH AUC from TB population was significantly lower than that of healthy volunteers (26% lower in TB adults, 42% lower in TB/HIV adults, 38% lower in TB pediatrics, and 61% lower in TB/HIV pediatrics). This great disparity in INH PK between healthy adult volunteers and TB patients demonstrate the necessity to adjust INH dose. Consequently, the current recommended INH dose regimen may not be sufficient in treating both TB adult and pediatric patients, and an increase in the INH dose may be needed.

In our analysis, many of the healthy adult volunteers took INH only, whereas TB patients took INH in combination with other antituberculosis drugs. This may have contributed to the observed difference in C_{max} and AUC between healthy adult volunteers and TB patients. However, the major pathway of INH metabolism is via NAT2 whereas RIF/EMB/PZA were eliminated through other pathways. Additionally, there are no known drug-drug interactions between INH and RIF/EMB/PZA that reduces INH concentrations [22]. Therefore, the impact of coadministration of other antituberculosis medications on C_{max} and AUC is likely negligible. Patients with TB/HIV may have some medications that may interact with antituberculosis drugs, but studies have found that the coadministration with efavirenz, tenofovir, emtricitabine, and nevirapine did not clinically affect the PK of INH [23, 24].

When the disposition of INH between pediatric and adult populations were compared, our meta-analysis showed that no difference was observed in INH PK between the TB adult patients and TB pediatric patients. This may indicate that TB does not impact INH PK due to age differences; therefore, this finding suggests that adult and pediatric INH dosing increase may be similar in magnitude if dose adjustment is warranted. When it comes to the revised WHO guideline for TB pediatrics, there is conflicting data about INH concentration. A study suggested that pediatric TB patients did not reach target range of INH concentration after taking INH 10 mg/kg body weight dosing [25]. On the contrary, another study suggested that a 10 mg/kg body weight dosing caused above normal range of C_{max} and AUC in pediatric TB patients, and recommended genotyping of acetylator status for optimization of INH dosing [26].

While there are significant differences in INH C_{max} and AUC observed between healthy adult volunteers and adults with TB/HIV and pediatrics with TB/HIV, our meta-analysis did not have a robust group of TB/HIV adult and pediatric patients; and therefore, these results and interpretations regarding TB/HIV patients should be extrapolated with caution. Nonetheless, healthcare providers should employ clinical judgments when treating the TB population.

For healthcare providers who are seeking to increase INH exposure for their patients, our meta-regression has shown that there is a dose proportional increase in INH C_{max} and AUC. However, with an INH dose increase there may be an increase in adverse events, although there are some data to support safety with high INH doses. Katiyar et al. reported that patients on INH dose range 16 – 18 mg/kg/day became sputum-negative 2.38 times faster than those patients who did not receive the high dose (5 mg/kg/day and placebo), and the high dose groups had more improved radiological imaging without the toxicity associated with INH [27]. A recent study of 59 TB patients were given a short course of INH dose range 5 – 15 mg/kg showed that 15.5% of patients had Grade 3 adverse events (pain, fever, dyspnea, pneumothorax, and anemia) and no cases higher than Grade 3; and the authors implied that these events were unlikely to be

related to study treatments. The 10 – 15 mg/kg INH doses were tolerable with pyridoxine co-administration [28]. High dose INH may be tolerable and safe, but clinicians should be cautious as more data is needed to further support this action.

NAT2 polymorphism should not be overlooked and must not be ignored given the results of this meta-analysis. Our meta-analysis showed a difference in INH PK due to NAT2 polymorphism and further stressed the need to test patients for NAT2 status. Patients with intermediate and fast NAT2 may have subtherapeutic exposure to INH with standard dosing, suggesting an INH dose of 800 mg/day, 500 mg/day, and 300 mg/day for fast, intermediate, and slow NAT2, respectively [29]. In a unique genotype-guided INH dosing study, patients were given either a standard INH dose (5 mg/kg) or an INH dose of 7.5 mg/kg, 5 mg/kg, and 2.5 mg/kg for fast, intermediate, and slow NAT2 genotype, respectively. A lower incidence of adverse events in the genotype-guided group were reported compared to the standard dosing (5 mg/kg) group, although it was not statistically significant. The rate of INH-induced liver injury was zero in the slow NAT2 genotype-guided group (n = 7) whereas seven out of nine slow NAT2 patients in the standard group experienced INH-induced liver injury [30]. Testing patients for NAT2 status may be beneficial, cost-effective, and improve health outcomes [31], as an INH dose lower than 6 mg/kg would put a majority of fast NAT2 patients at a disadvantage and a 3 mg/kg dose would be sufficient for slow NAT2 patients and reduce INH toxicity [32]. Since the NAT2 genotype prevalence differs between countries, it is recommended that each country conduct a profiling study of NAT2 from its own population [33]. Results from genotyping or phenotyping of NAT2 were shown to be consistent when obtained from patients [34], and these tests may be recommended prior to treating TB patients with INH to steer the course of TB treatment.

Conclusion

While vast inter-study heterogeneity was present throughout this meta-analysis, this by itself does not compromise our results and implications. Heterogeneity is inherent in all meta-analyses, along with other factors, such as incomplete data, data conversion, and interstudy variation. Regardless, we believe that our meta-analysis highlights the differences in INH PK between healthy adult volunteers and TB patients, TB/HIV patients, and the importance of NAT2 polymorphism. These key results can be useful reference points for healthcare providers when dosing INH for treating TB patients. Future studies that assess INH pharmacodynamic and safety outcomes in TB treatment with regards to high-dose INH and NAT2 polymorphism would be invaluable.

Funding

This work was supported in part by the Bill and Melinda Gates Foundation via a subaward of grant OPP1031105, awarded to the Critical Path to TB Regimens (CPTR) Initiative at the Critical Path Institute (C-Path).

Supplementary Data

Table S1 and Figure S1 are available as Supplementary Data.

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Table 1. Dose-normalized INH C_{max} for variables influencing its summary estimate.

Category	Number of study arms	Number of PK sets	C_{max} estimates*	95% CI	I^2 (%)	*P* value
Adults						
Healthy volunteers	97	1180	1.089	(0.969, 1.209)	99.50	
TB only	57	1638	0.698	(0.637, 0.759)	96.86	<0.0001[a]
TB/HIV	7	395	0.663	(0.567, 0.756)	90.95	<0.0001[a], 0.61[b]
Pediatrics						
TB only	30	636	0.618	(0.517, 0.718)	99.49	<0.0001[a], 0.18[b]
TB/HIV	5	119	0.498	(0.296, 0.699)	97.59	0.0025[a], 0.11[c], 0.34[d]

Dose-normalization of C_{max} indicated significant differences between healthy adult volunteers and TB patients. No statistical significance is observed between TB adult patients and pediatric patients. (a) difference from healthy adult volunteers (b) difference from TB adult patients (c) difference from TB/HIV adult patients (d) difference from TB pediatric patients.

*C_{max} estimates are in ((mg/L)/(mg/kg))

Table 2. Dose-normalized INH AUC for variables influencing its summary estimate.

Category	Number of study arms	Number of PK sets	AUC estimates*	95% CI	I^2 (%)	*P* value
Adults						
Healthy volunteers	109	1267	4.329	(3.818, 4.840)	98.94	
TB only	45	1077	3.183	(2.804, 3.563)	98.50	0.0006[a]
TB/HIV	4	189	2.503	(1.574, 3.431)	93.77	0.009[a], 0.18[b]
Pediatrics						
TB only	20	322	2.695	(2.315, 3.075)	95.53	0.0002[a], 0.16[b]
TB/HIV	3	90	1.674	(1.358, 1.990)	60.47	0.007[a], 0.22[c], 0.007[d]

Dose-normalization of AUC indicated significant differences between healthy adult volunteers and TB patients. No statistical significance is observed between TB adult patients and pediatric patients. (a) difference from healthy adult volunteers (b) difference from TB adult patients (c) difference from TB/HIV adult patients (d) difference from TB pediatric patients.

*AUC estimates are in ((mg·h/L)/(mg/kg))

Table 3. Effects of NAT2 polymorphism on dose-normalized C_{max} and AUC of all subjects

Category	**Number of study arms**	**Number of PK sets**	**C_{max} estimates***	**95% CI**	**I^2 (%)**	***P* value**
NAT2 status						
Slow	46	830	0.946	(0.861, 1.032)	98.03	
Intermediate	9	219	0.733	(0.640, 0.826)	88.80	0.017[a]
Fast	41	714	0.593	(0.511, 0.674)	98.46	<0.0001[a], 0.08[b]
Category	**Number of study arms**	**Number of PK sets**	**AUC estimates****	**95% CI**	**I^2 (%)**	***P* value**
NAT2 status						
Slow	42	528	5.494	(4.796, 6.192)	99.18	
Intermediate	7	157	2.305	(1.755, 2.854)	97.52	<0.0001[a]
Fast	35	497	2.017	(1.778, 2.255)	96.07	<0.0001[a], 0.27[b]

Dose-normalization of C_{max} and AUC stratified by NAT2 status indicated significant differences between subjects with slow NAT2 and intermediate/fast NAT2 status. (a) difference from subjects with slow NAT2 status (b) difference from subjects with intermediate NAT2 status.

*C_{max} estimates are in ((mg/L)/(mg/kg))

**AUC estimates are in ((mg·h/L)/(mg/kg))

Figure Legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for inclusion of isoniazid pharmacokinetic studies to February 2018.

Figure 2. Forest plot of dose-normalized AUC of adults with TB only. Study author, study arms, and year are listed. The black square and its size represent the mean and the sample size, with 95% CI as the horizontal line. The diamond is the summary estimate from all the study arms, and its expansion represents the 95% CI. The red-dotted line is a reference line with regards to the summary estimate.

Figure 3. Forest plot of dose-normalized AUC of pediatrics with TB only. Study author, study arms, and year are listed. The black square and its size represent the mean and the sample size, with 95% CI as the horizontal line. The diamond is the summary estimate from all the study arms, and its expansion represents the 95% CI. The red-dotted line is a reference line with regards to the summary estimate. **Figure 4.** a) Forest plot of dose-normalized AUC of adults with TB/HIV. b) Forest plot of dose-normalized AUC of pediatrics with TB/HIV. Study author, study arms, and year are listed. The black square and its size represent the mean and the sample size, with 95% CI as the horizontal line. The diamond is the summary estimate from all the study arms, and its expansion represents the 95% CI. The red-dotted line is a reference line with regards to the summary estimate.

Figure 5. a) Meta-regression of C_{max} with dose (mg/kg) as a covariate. A linear relationship is present with C_{max} increasing as dose increases. Regression line is shown with equation. b) Meta-regression of AUC with dose (mg/kg) as a covariate. A linear relationship is present with AUC increasing as dose increases. Regression line is shown with equation, with corresponding p-value and R^2. Each circle represents a study arm and its size correlates to the sample size.

Figure 1.

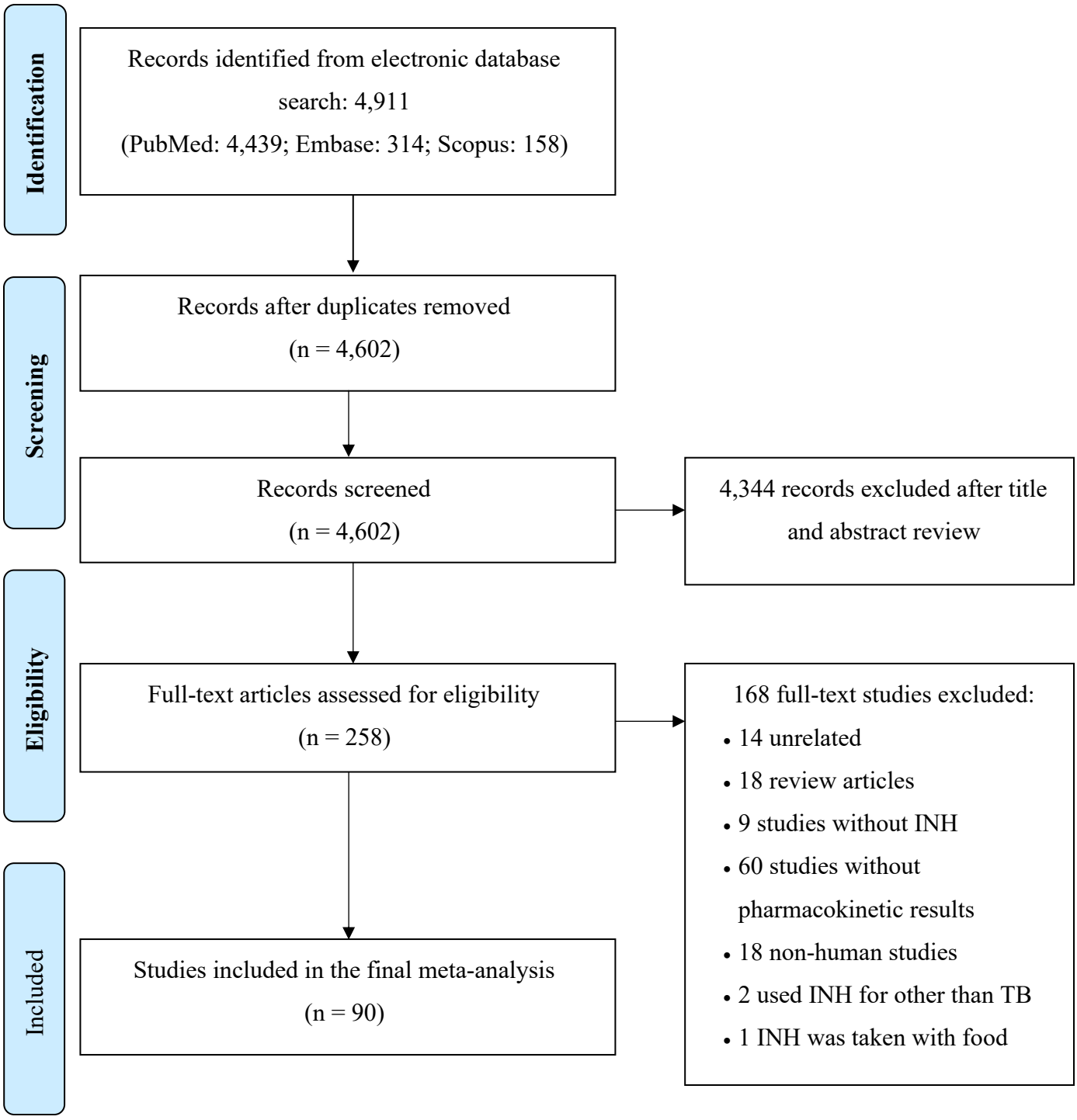

Identification
Records identified from electronic database search: 4,911
(PubMed: 4,439; Embase: 314; Scopus: 158)
Screening
Records after duplicates removed
(n = 4,602)
Records screened
(n = 4,602)
4,344 records excluded after title and abstract review
Eligibility
Full-text articles assessed for eligibility
(n = 258)
168 full-text studies excluded:
• 14 unrelated
• 18 review articles
• 9 studies without INH
• 60 studies without pharmacokinetic results
• 18 non-human studies
• 2 used INH for other than TB
• 1 INH was taken with food
Included
Studies included in the final meta-analysis
(n = 90)

Figure 2.

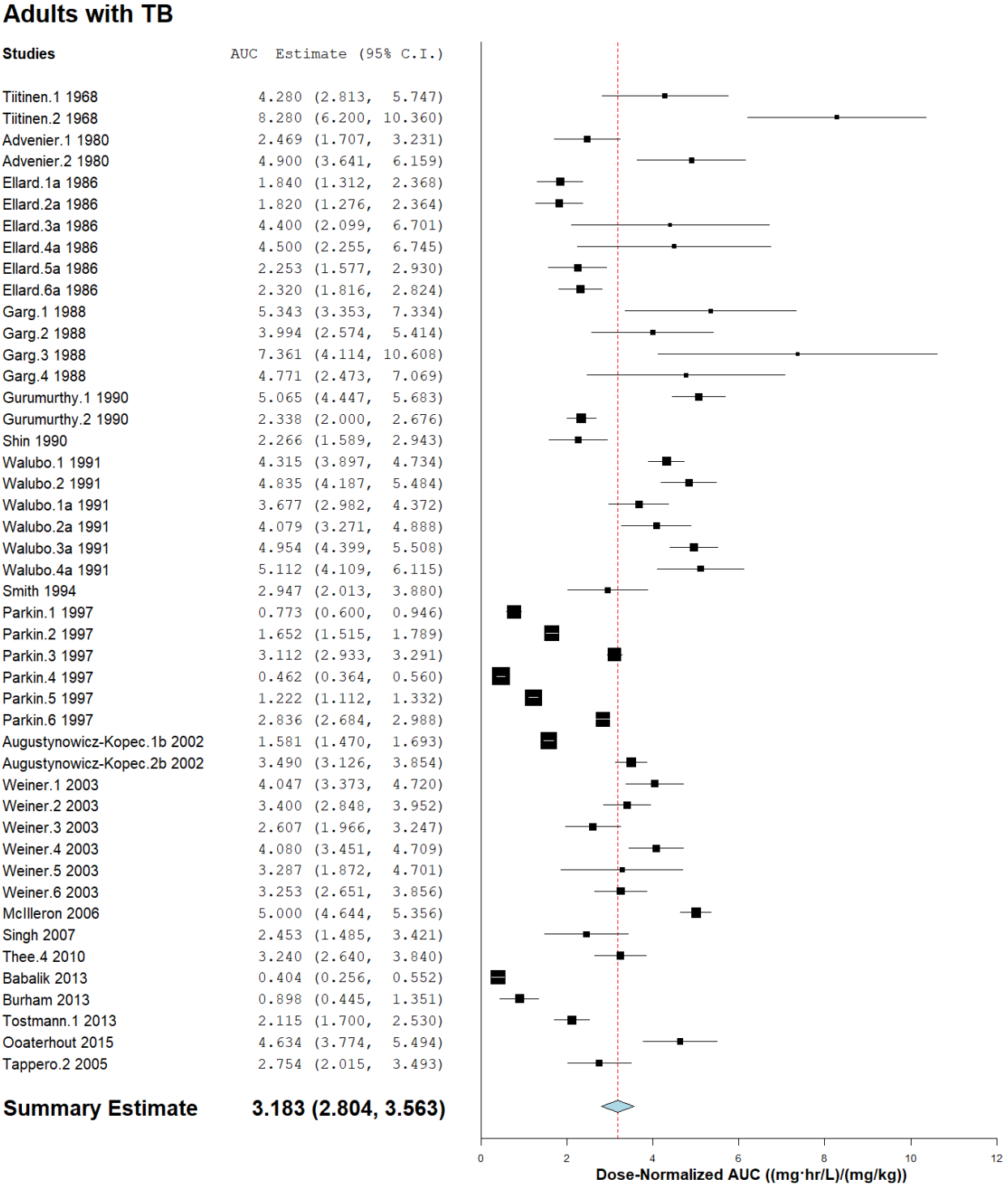

Adults with TB
Studies
AUC Estimate (95% C.I.)
Tiitinen.1 1968 4.280 (2.813, 5.747)
Tiitinen.2 1968 8.280 (6.200, 10.360)
Advenier.1 1980 2.469 (1.707, 3.231)
Advenier.2 1980 4.900 (3.641, 6.159)
Ellard.1a 1986 1.840 (1.312, 2.368)
Ellard.2a 1986 1.820 (1.276, 2.364)
Ellard.3a 1986 4.400 (2.099, 6.701)
Ellard.4a 1986 4.500 (2.255, 6.745)
Ellard.5a 1986 2.253 (1.577, 2.930)
Ellard.6a 1986 2.320 (1.816, 2.824)
Garg.1 1988 5.343 (3.353, 7.334)
Garg.2 1988 3.994 (2.574, 5.414)
Garg.3 1988 7.361 (4.114, 10.608)
Garg.4 1988 4.771 (2.473, 7.069)
Gurumurthy.1 1990 5.065 (4.447, 5.683)
Gurumurthy.2 1990 2.338 (2.000, 2.676)
Shin 1990 2.266 (1.589, 2.943)
Walubo.1 1991 4.315 (3.897, 4.734)
Walubo.2 1991 4.835 (4.187, 5.484)
Walubo.1a 1991 3.677 (2.982, 4.372)
Walubo.2a 1991 4.079 (3.271, 4.888)
Walubo.3a 1991 4.954 (4.399, 5.508)
Walubo.4a 1991 5.112 (4.109, 6.115)
Smith 1994 2.947 (2.013, 3.880)
Parkin.1 1997 0.773 (0.600, 0.946)
Parkin.2 1997 1.652 (1.515, 1.789)
Parkin.3 1997 3.112 (2.933, 3.291)
Parkin.4 1997 0.462 (0.364, 0.560)
Parkin.5 1997 1.222 (1.112, 1.332)
Parkin.6 1997 2.836 (2.684, 2.988)
Augustynowicz-Kopec.1b 2002 1.581 (1.470, 1.693)
Augustynowicz-Kopec.2b 2002 3.490 (3.126, 3.854)
Weiner.1 2003 4.047 (3.373, 4.720)
Weiner.2 2003 3.400 (2.848, 3.952)
Weiner.3 2003 2.607 (1.966, 3.247)
Weiner.4 2003 4.080 (3.451, 4.709)
Weiner.5 2003 3.287 (1.872, 4.701)
Weiner.6 2003 3.253 (2.651, 3.856)
McIlleron 2006 5.000 (4.644, 5.356)
Singh 2007 2.453 (1.485, 3.421)
Thee.4 2010 3.240 (2.640, 3.840)
Babalik 2013 0.404 (0.256, 0.552)
Burham 2013 0.898 (0.445, 1.351)
Tostmann.1 2013 2.115 (1.700, 2.530)
Ooaterhout 2015 4.634 (3.774, 5.494)
Tappero.2 2005 2.754 (2.015, 3.493)
Summary Estimate 3.183 (2.804, 3.563)
0
2
4
6
8
10
12
Dose-Normalized AUC ((mg·hr/L)/(mg/kg))

Figure 3.

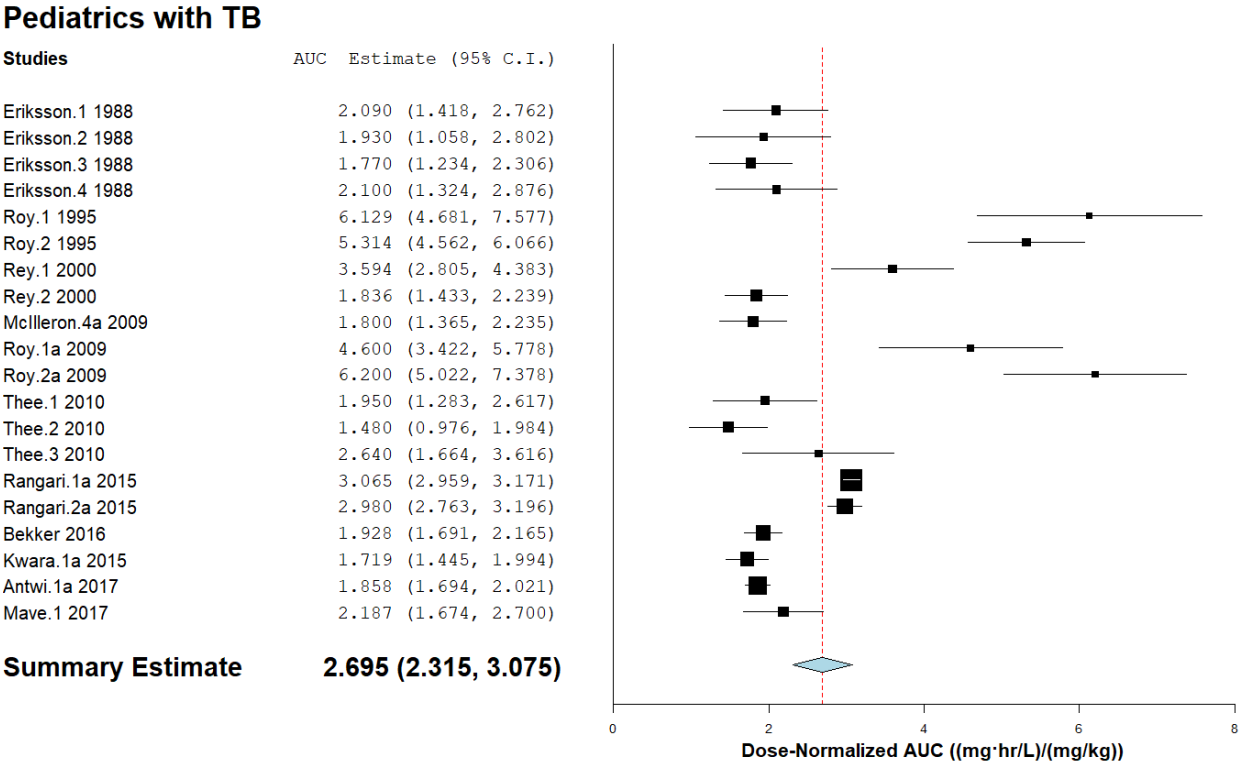
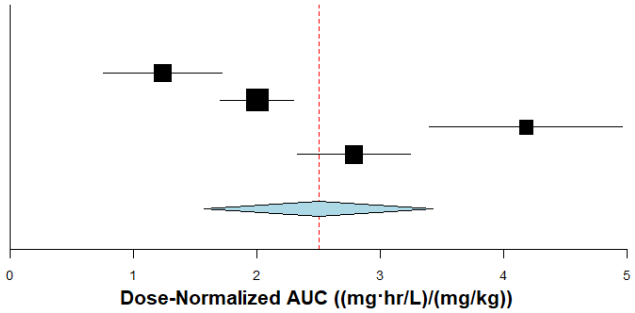

Pediatrics with TB
Studies
AUC Estimate (95% C.I.)
Eriksson.1 1988 2.090 (1.418, 2.762)
Eriksson.2 1988 1.930 (1.058, 2.802)
Eriksson.3 1988 1.770 (1.234, 2.306)
Eriksson.4 1988 2.100 (1.324, 2.876)
Roy.1 1995 6.129 (4.681, 7.577)
Roy.2 1995 5.314 (4.562, 6.066)
Rey.1 2000 3.594 (2.805, 4.383)
Rey.2 2000 1.836 (1.433, 2.239)
McIlleron.4a 2009 1.800 (1.365, 2.235)
Roy.1a 2009 4.600 (3.422, 5.778)
Roy.2a 2009 6.200 (5.022, 7.378)
Thee.1 2010 1.950 (1.283, 2.617)
Thee.2 2010 1.480 (0.976, 1.984)
Thee.3 2010 2.640 (1.664, 3.616)
Rangari.1a 2015 3.065 (2.959, 3.171)
Rangari.2a 2015 2.980 (2.763, 3.196)
Bekker 2016 1.928 (1.691, 2.165)
Kwara.1a 2015 1.719 (1.445, 1.994)
Antwi.1a 2017 1.858 (1.694, 2.021)
Mave.1 2017 2.187 (1.674, 2.700)
Summary Estimate 2.695 (2.315, 3.075)
0
2
4
6
8
Dose-Normalized AUC ((mg·hr/L)/(mg/kg))

Figure 4.

a)

Adults with TB/HIV

Studies	AUC Estimate (95% C.I.)
Weiner.1a 2005	1.233 (0.753, 1.713)
Weiner.2a 2005	2.000 (1.704, 2.296)
Bhatt 2013	4.184 (3.401, 4.967)
Tappero.1 2005	2.785 (2.325, 3.244)
Summary Estimate	**2.503 (1.574, 3.431)**



b)

Pediatrics with TB/HIV

Studies	AUC Estimate (95% C.I.)
Kwara.2a 2015	1.408 (1.116, 1.699)
Antwi.2a 2017	1.842 (1.575, 2.109)
Mave.2 2017	1.832 (1.296, 2.368)
Summary Estimate	**1.674 (1.358, 1.990)**

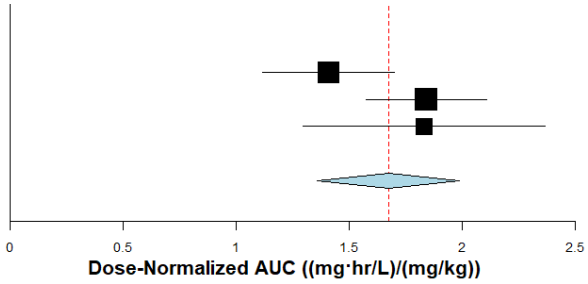
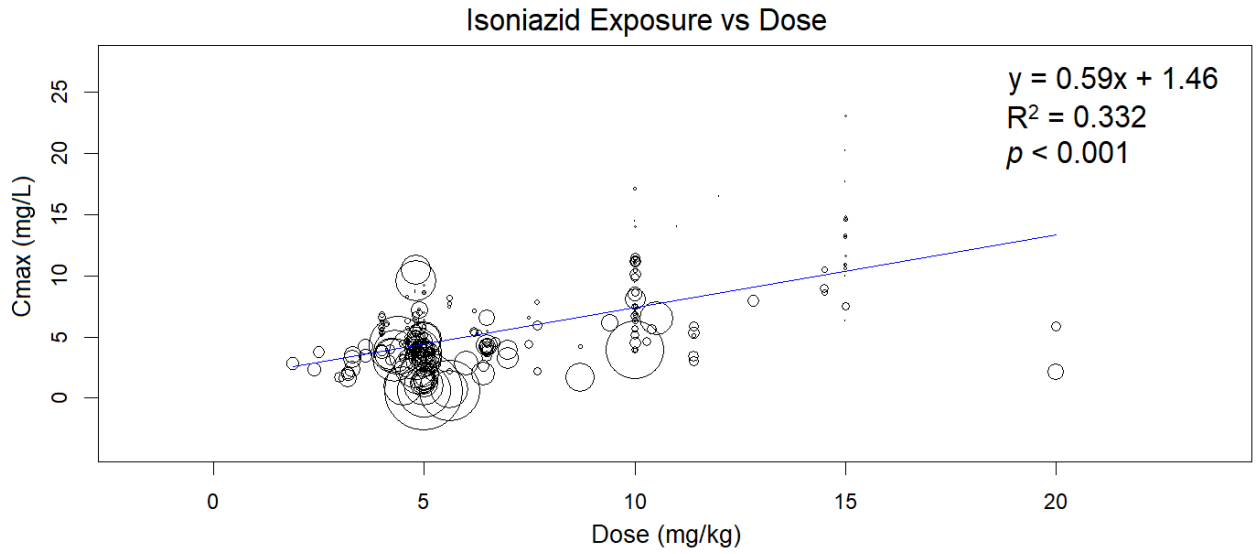
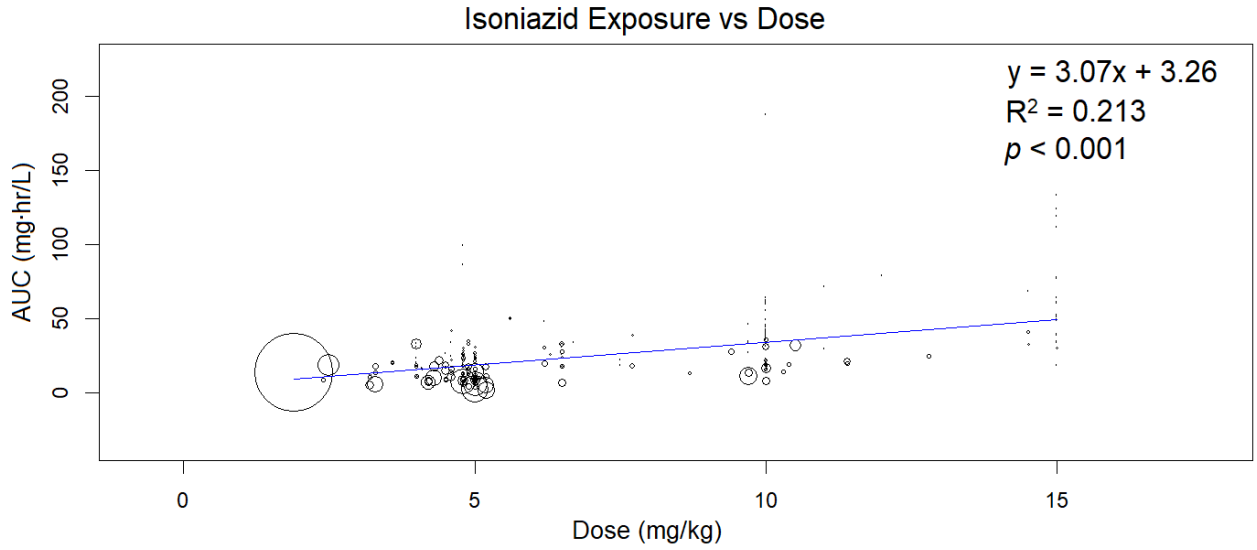


Figure 5.

a)


Isoniazid Exposure vs Dose
y = 0.59x + 1.46
R² = 0.332
p < 0.001
Cmax (mg/L)
0
5
10
15
20
25
0
5
10
15
20
Dose (mg/kg)

b)


Isoniazid Exposure vs Dose
y = 3.07x + 3.26
R² = 0.213
p < 0.001
AUC (mg·hr/L)
0
50
100
150
200
0
5
10
15
Dose (mg/kg)