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ORIGINAL ARTICLE

Benchmark dose modeling for epidemiological dose–response assessment using prospective cohort studies

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Abstract

Benchmark dose (BMD) methodology has been employed as a default dose–response modeling approach to determine the toxicity value of chemicals to support regulatory chemical risk assessment. Especially, a relatively standardized BMD analysis framework has been established for modeling toxicological data regarding the formats of input data, dose–response models, definitions of benchmark response, and model uncertainty consideration. However, the BMD approach has not been well developed for epidemiological data mainly because of the diverse designs of epidemiological studies and various formats of data reported in the literature. Although most of the epidemiological BMD analyses were developed to solve a particular question, the methods proposed in two recent studies are able to handle cohort and case–control studies using summary data with consideration of adjustments for confounders. Therefore, the purpose of the present study is to investigate and compare the "effective count"-based BMD modeling approach and adjusted relative risk (RR)-based BMD analysis approach to identify an appropriate BMD modeling framework that can be generalized for analyzing published data of prospective cohort studies for BMD analysis. The two methods were applied to the same set of studies that investigated the association between bladder and lung cancer and inorganic arsenic exposure for BMD estimation. The results suggest that estimated BMDs and BMDLs are relatively consistent; however, with the consideration of established common practice in BMD analysis, modeling adjusted RR values as continuous data for BMD estimation is a more generalizable approach harmonized with the BMD approach using toxicological data.

KEYWORDS
arsenic exposure, Bayesian analysis, benchmark dose, bladder cancer, epidemiological risk assessment, lung cancer

1 | INTRODUCTION

Benchmark dose (BMD) methodology (Shao & Shapiro, 2018; US Environmental Protection Agency. Risk Assessment Forum, 2012) is now being employed as a default dose–response modeling approach to determine the toxicity value of chemicals to support regulatory chemical risk assessment. The BMD method has been continuously developed and improved since the proposal of the BMD concept (Crump, 1984) and has become a relatively mature and standardized modeling framework primarily for toxicological data. It is critical to note that the BMD method in risk assessment is primarily applied to analyze published toxicological dose–response data (i.e., raw individual animal data are summarized using various statistics for each dose group), even though the BMD method is completely capable of modeling individual dose–response data (Shao & Shapiro, 2018). The standardization of the BMD modeling framework is mainly reflected through four important aspects. First, well-defined format of input data clarifies the data requirements for BMD

modeling. For example, the dose level, the numbers of total tested animals, and affected animals are the three required quantities for modeling dichotomous data, whereas for continuous data, the dose level, number of tested animals in each dose group, mean, and standard deviation of the responses in each dose group are the four required quantities. Second, empirical models representing various dose–response shapes are well developed for dichotomous and continuous data. Third, the extra- or added-risk-based benchmark response (BMR) for dichotomous data as well as the central tendency- or distribution tail-based BMR definition for continuous data (Shao & Shapiro, 2018) are widely accepted. Finally, the "best model" approach or more recently proposed model averaged BMD estimation method is employed to address model uncertainty in BMD/BMD level (BMDL) estimation. These strategies mentioned above make the BMD analysis for toxicological data relatively easy to perform and interpret. On the other hand, a BMD modeling framework has not been properly established for epidemiological data because of the complexity of epidemiological studies. Compared to toxicological studies, epidemiological studies are more complicated with respect to study design (e.g., cohort and case–control studies), exposure measurement (e.g., expressed in ranges), and expression of adversity (e.g., odds ratios [ORs] and relative risks [RRs]). A few recent studies applied different strategies to estimate BMDs from epidemiological data. Kullar et al. (2019) applied the BMD method to estimate water manganese levels associated with predetermined levels of cognitive impairment in children. Individual tap water manganese concentration and performance IQ data (which were adjusted for potential confounders or important determinants) of 630 children were used as input data for BMD estimation. US FDA's Arsenic in Rice and Rice Products Risk Assessment Report (US Food and Drug Administration [US FDA], 2016) proposed to model incidence ratios of exposure groups as dichotomous data reported in prospective cohort studies for analyzing BMD where confounding covariates were taken into account by using adjusted numbers of cases in BMD modeling. Allen et al. (2020b) introduced the idea of using "effective counts" that were adjusted counts for covariates based on the adjusted ORs or RRs of exposure groups reported in the literature for BMD analysis. Shao et al. (2021) applied the BMD modeling strategy for summary continuous data to model adjusted ORs or RRs of exposure groups as the continuous response for BMD estimation.

These BMD estimation methods briefly described above have different features and adaptabilities. The BMD modeling approach employed in Kullar et al. (2019) was only suitable when raw epidemiological data are available, so it is a generally applicable approach in the chemical risk assessment that heavily relies on published summary data. The US FDA (2016) approach very precisely follows the BMD framework developed for toxicological data with the adjustment for potential confounding factors; however, this approach is specifically designed for cohort studies (not for case–control studies) where incidence ratios are available. The methods presented in Allen et al. (2020b) and Shao et al. (2021) are both able to handle cohort and case–control studies using summary data reported in epidemiological studies with the consideration of adjustments for confounders. Therefore, the purpose of the present study is to investigate and compare the "effective count"-based BMD modeling approach (Allen et al., 2020b) and adjusted RR-based BMD analysis approach (Shao et al., 2021) to identify an appropriate BMD modeling framework that can be generalized for analyzing published epidemiological data for BMD analysis. With the goal of making the BMD methodology as consistent as possible between toxicological and epidemiological studies, the "better" approach will be selected based on its alignment with the four components of a BMD modeling framework mentioned above. When handling epidemiological data that have been summarized into exposure ranges, uncertainty in exposure should be properly addressed and can be applied to the approaches being compared with no differences. Consequently, the approaches for exposure level selection and modeling exposure uncertainty are outside the scope of the present study. High-quality epidemiological data are always preferred over toxicological data in risk assessment for reference dose derivation because no animal to human extrapolation is needed. Therefore, a standardized and generalized BMD modeling framework for the epidemiological study is critically needed and may have a significant impact on regulatory risk assessment. In this study, we will focus on the comparison using dose–response data from prospective cohort studies, whereas the investigation for case–control studies will be presented in another publication. The rest of this article is organized as follows: Section 2 describes the arsenic exposure dataset employed in our analysis. We detail the methods to pretreat and analyze such data, based on dichotomous and continuous BMD models (henceforth, simply dichotomous and continuous BMD models). In Section 3, we compare both models and show the main outcomes of our analysis, exploring their statistical association. We discuss further expansions and limitations of our approach in Section 4.

2 | MATERIALS AND METHODS

In this section, we introduce the structure and representation of prospective cohort data used in this study to compare two different modeling approaches for BMD estimation from epidemiological studies. These two modeling methods, that is, model the epidemiological dose–response data (1) as dichotomous data (Section 2.3.1) or (2) as continuous data (Section 2.3.2), are discussed here as well.

2.1 | Basics for epidemiological data representation

Throughout the article, we make use of the notation introduced in Lash et al. (2021, Chapters 16–18) for categorical

(a) Contingency tables for person-time data

	Exposed	Bkgnd Exp	Total
Cases	A_1	A_0	M_1
Person-time	T_1	T_0	T

(a.1) Format for two exposure groups

	Exposed	Bkgnd Exp	Total
Cases	$A_{G-1} \ldots A_i \ldots A_1$	A_0	M_1
Person-time	$T_{G-1} \ldots T_i \ldots T_1$	T_0	T

(a.2) Format for multiple exposure groups

(b) Contingency tables for pure count data

	Exposed	Bkgnd Exp	Total
Cases	A_1	A_0	M_1
Noncases	B_1	B_0	M_0
Total	N_1	N_0	N

(b.1) Format for two exposure groups

	Exposed	Bkgnd Exp	Total
Cases	$A_{G-1} \ldots A_i \ldots A_1$	A_0	M_1
Noncases	$B_{G-1} \ldots B_i \ldots B_1$	B_0	M_0
Total	$N_{G-1} \ldots N_i \ldots N_1$	N_0	N

(b.2) Format for multiple exposure groups

FIGURE 1 Common notation for contingency tables categorizing epidemiological data. Tables on the left side (a: a.1 and a.2) are employed to represent person–time data, whereas those on the right side (b: b.1 and b.2) are used for pure count data. Examples for two exposure groups or a general number of G groups are provided in subtables.

statistics purposes, except for one case that we detail below. In particular, we represent absolute frequencies of person–time data and pure count data by the contingency tables (a) and (b) shown in Figure 1. Each of these tables is composed by two subtables, outlining the format used for two exposure groups (exposed and background exposure) and multiple exposure groups (up to a number G). In these tables, we express cases by the letter A, number of subjects by N, and person–time by T. The latter quantities usually appear as denominators in standard epidemiological ratio-based measures: We will conform to such notation as well in the formulas provided here. The superscripts e and r refer to effective and raw (original) counts; they also signal if an epidemiological measure is adjusted or unadjusted. The subscript i marks each of the G exposure groups, with $i = 0$ denoting the background exposure (Bkgnd Exp)/baseline/referent group, as it may be defined in accordance with the context where the latter is used. In this article, we use two different cohort study data types: incidence rate and cumulative incidence cohort studies. They are usually characterized by two different kinds of risk measures, as it will be now detailed. However, for a more complete description of such studies, we again refer the reader to Lash et al. (2021, Chapter 7).

Whatever person–time or pure count data to consider, it is usual to introduce ratio measures based on such data. Should we identify person–time data as the denominator of interest in our computations (as is generally the case when analyzing incidence rate cohort studies), we tend to assume a Poisson model to fit the number of cases occurring in a stationary population followed for a fixed time span. This leads to defining a ratio measure for a given exposure group as a ratio, usually named incidence rate ratio (IRR) or simply IR, as Lash et al. (2021) do, whose maximum likelihood estimate reads as

$$\mathrm{IR}_i = \frac{A_i}{T_i} \Big/ \frac{A_0}{T_0}, \tag{1}$$

and with the standard error (SE) of its logarithmic measure being:

$$\mathrm{SE}\left[\log\left(\mathrm{IR}_i\right)\right] = \sqrt{\frac{1}{A_i} + \frac{1}{A_0}}. \tag{2}$$

On the other side, should we consider the number of subjects as the primary denominator in our computations (as it naturally lands for cumulative incidence cohort studies), we favor constructing a Binomial model for the number of cases occurring out of a fixed number of subjects. This leads to defining a ratio measure for a given exposure group as a risk ratio, usually known as RR and named RR, whose maximum likelihood estimate reads as

$$\mathrm{RR}_i = \frac{A_i}{N_i} \Big/ \frac{A_0}{N_0}, \tag{3}$$

and with the SE of its logarithmic measure being

$$\mathrm{SE}\left[\log\left(\mathrm{RR}_i\right)\right] = \sqrt{\frac{1}{A_i} - \frac{1}{N_i} + \frac{1}{A_0} - \frac{1}{N_0}}. \tag{4}$$

Instead of conforming to such notation, several epidemiological studies most of the times employ IR—derived through Cox proportional hazards regression models (e.g., Chen et al., 2010a)—but use RR as a symbol. Differently from Lash et al. (2021) but as already done in Allen et al. (2020b), in this

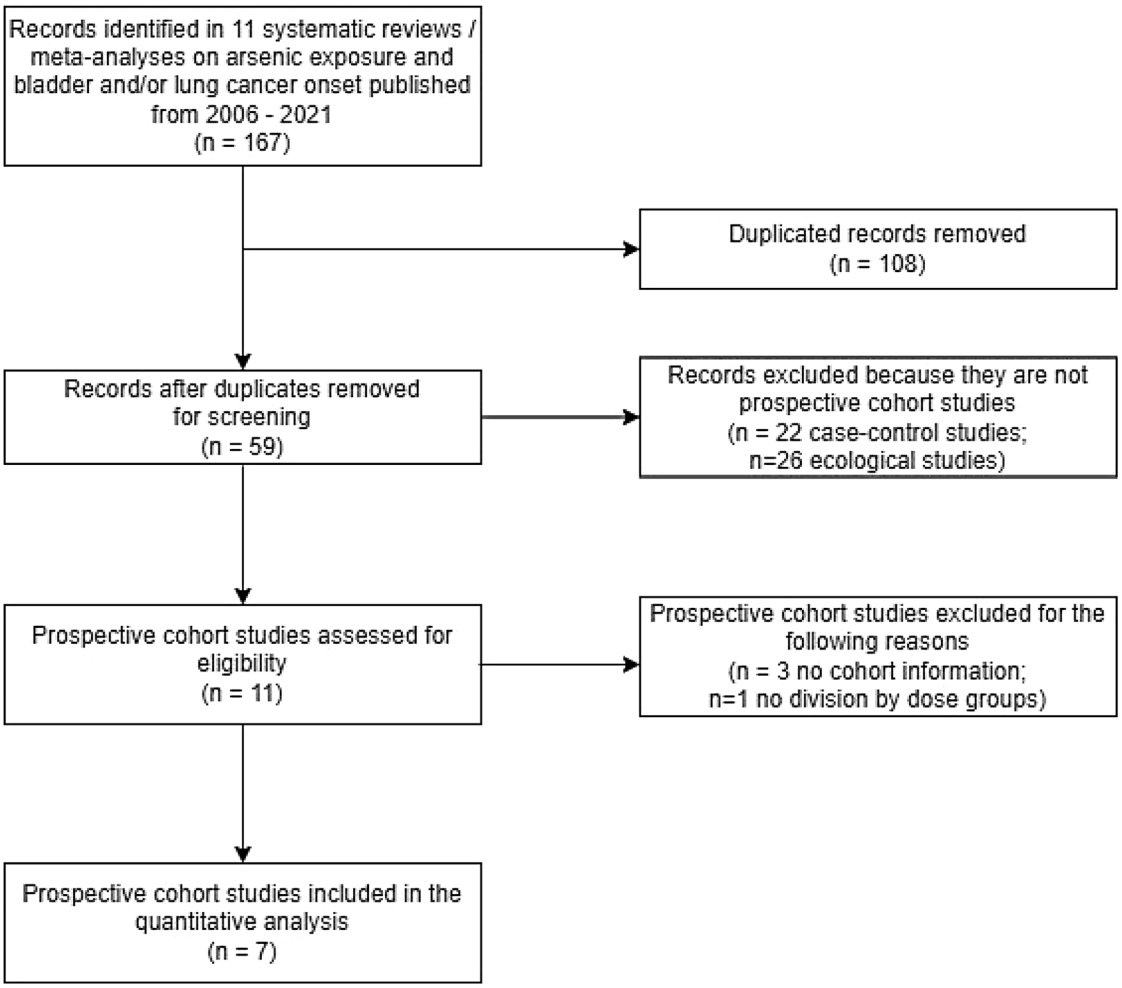


FIGURE 2 Flowchart for the identification of prospective cohort studies to be considered for the testing dataset. It maps out the number of records identified, included and excluded, and the reasons for exclusions.

article, we will abide to this convention, in line with Orsini et al. (2011) who change the definition of the RR measure in agreement with the type of summarized data.

2.2 | Dose–response data from prospective cohort studies

To compare the continuous and dichotomous BMD models (see Section 2.3), we considered a list of 11 systematic reviews/meta-analyses published in the last 15 years (2006–2021) and focused on the coupling between arsenic exposure by water ingestion or inhalation and onset of various forms of tumors, principally bladder and lung cancer, as they represent the majority of loci in neoplastic formations recorded in observational studies, next to kidney and liver tumors. Therefore, we limited our analysis to such types of cancer, and from these systematic reviews/meta-analyses, we extracted data only belonging to prospective cohort studies (see Figure 2).

Information on extracted data is reported in Table 1: They are all incidence rate cohort studies and all account for data coming from the Taiwanese area, which has a research record in conducting epidemiological studies centered on arsenic hazard (Morales et al., 2000; Wu et al., 1989).

From the same initial list, other five studies were reported as prospective cohort studies but were subsequently discarded, because not fitting some of the requirements needed for our analysis. More specifically, Baastrup et al. (2008) (Denmark) did not provide any division by dose groups; D'Ippoliti et al. (2015) (Italy) and Sawada et al. (2013) (Japan) presented an aggregated clustering between men and women for exposure purposes but no detailed information pertaining to the general cohort (especially that related to the dosage); and Chen and Ahsan (2004) (Bangladesh) shared the same previous issue and furthermore its analysis employed no internal referent groups, as the dose-specific RR estimates used in predicting risks were derived from a Taiwanese study whose data were not retrievable. Raw data (next to from the selected prospective cohort studies) are shown in the next section, shown in Tables 2 and 3.

TABLE 1 Prospective cohort studies selection.

Systematic review / meta-analysis ↓	Prospective cohort study →	Bogen et al. (2014)	Chen et al. (2010a)	Chen et al. (2010b)	Chiou et al. (1995)	Chiou et al. (2001)	Chung et al. (2013)	Huang et al. (2008)
Allen et al. (2020a)		–	B	L	–	–	–	–
Boffetta and Borron (2019)		–	B	L	–	–	B	–
Christoforidou et al. (2013)		–	B	L	–	B	–	–
Chu and Crawford-Brown (2006)		–	–	–	B, L	B	–	B
Lamm et al. (2015)		L	B	L	–	–	–	–
Lamm et al. (2021)		L	B	L	–	–	–	–
Lynch et al. (2017)		–	B	L	B, L	–	–	B
Saint-Jacques et al. (2014)		–	B	L	B, L	B	B	B
Shao et al. (2021)		–	B	L	–	–	–	–
Tsuji et al. (2014)		–	B	L	–	–	–	–
Tsuji et al. (2019)		–	B	L	–	–	–	–

Note: On the left, the first column shows a list of the principal systematic reviews/meta-analyses conducted in the last 15 years (2006–2021) and related to the binding between arsenic exposure and bladder and lung cancer. The selected prospective cohort studies are reported in the first row. B (bladder) and L (lung) letters mark the studies' object.

2.3 | BMD modeling methods for epidemiological data

This subsection is further divided into four parts: In the first two parts, we provide a description of the models; we employ to analyze dichotomous and continuous data, to then focus on the pretreatment of the dose (adjusted exposure midpoint computations) and of the response (BMR calibration).

2.3.1 | Model epidemiological data as dichotomous data

This model works in two steps. Initially, data are pretreated to derive the *effective counts* (Allen et al., 2020b), that is, the effective number of cases A and of subjects N obtained as we consider the RR and the interval of its SEs both varying with respect to the different dose groups. As we detail below, computations are performed differently if the input data come from incidence rate or cumulative incidence cohort studies, but the model still requires the same quantities, that is, for each dose group, the number of cases A, the number of subjects N, and the RR including its upper and lower bound at a given statistical significance level. Despite some theoretical assumptions that we make on the person–time T, the latter are not explicitly entering the required computations. Eventually, the effective counts are modeled as dichotomous data to calculate BMDs as outlined in Shao and Shapiro (2018).

Incidence rate cohort studies: We follow Allen et al. (2020b)'s effective counts computations by preliminarily setting $A_0^e = A_0^r$ and $T_0^e = T_0^r$, that is, the referent group serves as an invariant in our analysis. Then, all the subsequent computations hold for $i > 0$. Assuming a significance level of ff = 5%, we have

$$\mathrm{SE}\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{L}} = \frac{1}{Z_{0.975}} \cdot \log\left(\frac{\mathrm{RR}_i}{\mathrm{RR}_i^{\mathrm{L}}}\right), \tag{5}$$

$$\mathrm{SE}\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{U}} = \frac{1}{Z_{0.975}} \cdot \log\left(\frac{\mathrm{RR}_i^{\mathrm{U}}}{\mathrm{RR}_i}\right), \tag{6}$$

where $\mathrm{RR}_i^{\mathrm{L}}$ and $\mathrm{RR}_i^{\mathrm{U}}$, respectively, represent the lower and upper bound of the confidence interval at the 95% level for the adjusted RR_i of the G_ith group.

To highlight the fact that we are working on an adjusted measure, and RR_i should more correctly read as RR_i^e. However, if not manifestly stated, henceforth, we omit this superscript for simplicity. Furthermore, if 90% or 99% instead of most-commonly used 95% CI was reported, $Z_{0.975}$ in the formula needs to be modified as $Z_{0.95}$ or $Z_{0.995}$. Combining the latter formulas with Equation (2), we can explicit effective cases as

$$A_i^e = \frac{1}{2} \cdot \left(\left\{ \mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{L}} - \frac{1}{A_0^r} \right\}^{-1} + \left\{ \mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{U}} - \frac{1}{A_0^r} \right\}^{-1} \right), \tag{7}$$

in which we average by an arithmetic mean the computations done considering both $\mathrm{RR}_i^{\mathrm{L}}$ and $\mathrm{RR}_i^{\mathrm{U}}$ terms. In addition

TABLE 2 Dose–response incidence rate cohort studies and related data for bladder cancer.

Study (location)	Exposure concentration group (μg/L)	Water intake rate (L/day)	Adjusted exposure midpoint (μg/L)	Adjusted RR (95% CI)	Cases/non-cases		Number of subjects	
					Raw	Effective	Raw	Effective
Chen et al. (2010a) (NE Taiwan)	<10	3.85	9.63	1	5/2283	5/2283	2288	2288
	10–49.9		57.75	1.66 (0.53–5.21)	8/2085	7.15/1863.47	2093	1870.62
	50–99.9		144.38	2.42 (0.69–8.54)	5/902	4.72/851.49	907	856.21
	100–299.9		385.00	4.13 (1.32–12.90)	8/901	7.24/815.40	909	822.64
	≥300		866.25	7.80 (2.64–23.10)	11/680	9.42/582.33	691	591.75
Chiou et al. (1995)[a] (SW Taiwan)	<50	3.85	48.13	1	6/610.99	6/610.99	616.99	616.99
	50–70		115.50	1.80 (0.60–5.30)	7/542.44	7.04/545.54	549.44	552.58
	>70		202.13	3.30 (1.00–11.10)	7/530.17	4.76/360.52	537.17	365.28
Chiou et al. (2001)[a] (NE Taiwan)	<10	3.85	9.63	1	3/2818.99	3/2818.99	2821.99	2821.99
	10–50		57.75	1.50 (0.30–8.00)	3/2364.81	2.73/2151.98	2367.81	2154.71
	50–100		144.38	2.20 (0.40–13.70)	2/1063.76	2.11/1122.27	1065.76	1124.38
	>100		288.75	4.80 (1.20–19.40)	7/1839.43	5.86/1539.87	1846.43	1545.73
Chung et al. (2013)[a,b,c] (SW Taiwan)	<50	3.85	48.13	1	1/1071.98	1/1071.98	1072.98	1072.98
	50–710		731.50	4.35 (0.56–33.52)	15/86.52	11.17/64.43	101.52	75.60
	>710		2050.13	7.22 (0.95–55.04)	22/366.50	13.82/230.23	388.50	244.05
Huang et al. (2008) (SW Taiwan)	<400	3.85	385.00	1	1/175	1/175	176	176
	400–700		1058.75	5.20 (0.70–39.80)	14/263	17.07/320.67	277	337.74
	700–900		1540.00	6.70 (0.80–53.40)	9/130	6.96/100.53	139	107.49
	>900		2598.75	6.50 (0.80–53.10)	7/112	6.88/110.08	119	116.96

[a]Number of subjects estimated from person–years at risk (for Chung et al. (2013), data provided by Chen et al. (1996)).
[b]Hazard ratio (*HR*) reported, instead of *RR*.
[c]Mortality study.

to what previously shown in Allen et al. (2020b), we complement our analysis by looking at T_i^e and N_i^e terms. The former constitutes one of the necessary elements to compute RR_i measures, as outlined in Equation (1). However, the very nature of the related Equation (2) makes the computation of T_i^e unfeasible, as such terms do not appear in the definition of SE[log(RR_i)], differently from what occurs with N_i^e terms in Equation (4) used in cumulative incidence cohort studies (see next paragraph). Therefore, we set $T_i^e = T_i^r$, that is, person–time stay unchanged whether we consider adjusted or unadjusted RR_i measures. With respect to N_i^e terms, we instead acknowledge that they do not enter the computation of the RR_i measures (hence, they cannot be retrieved from Equations (1) and (2) ab initio). Being independent from them, we thus assume N_i^e terms to vary proportionally via a linear projection as RR_i measures do when adjusted. Clearly, several other projections could have been taken into account in modeling such a variation but a linear one represents a cautious assumption that could be also considered a first approximation to nonlinear others. More explicitly,

TABLE 3 Dose–response incidence rate cohort studies and related data for lung cancer.

Study (location)	Exposure concentration group (μg/L)	Water intake rate (L/day)	Adjusted exposure midpoint (μg/L)	Adjusted RR (95% CI)	Cases/non-cases		Number of subjects	
					Raw	Effective	Raw	Effective
Bogen et al. (2014) (NE Taiwan)	0–1	3.85	0.96	1	32/1039	32/1039	1071	1071
	1–10		10.59	0.57 (0.33–0.97)	23/1348	22.56/1322.21	1371	1344.77
	10–49.9		57.75	0.73 (0.47–1.15)	47/1980	48.22/2031.40	2027	2079.62
	50–99.9		144.38	0.68 (0.38–1.19)	19/861	18.73/848.76	880	867.49
	100–299.9		385.00	1.08 (0.65–1.80)	17/856	27.57/1388.23	873	1415.80
	≥300		866.25	1.50 (0.95–2.60)	30/636	32.21/682.85	666	715.06
Chen et al. (2010b) (NE Taiwan)	<10	3.85	9.63	1	48/2240	48/2240	2288	2288
	10–49.9		57.75	1.10 (0.74–1.63)	51/2042	50.64/2027.59	2093	2078.23
	50–99.9		144.38	0.99 (0.59–1.68)	20/887	19.84/879.90	907	899.74
	100–299.9		385.00	1.54 (0.97–2.46)	28/881	28.16/886.03	909	914.19
	≥300		866.25	2.25 (1.43–3.55)	31/660	30.33/645.74	691	676.07
Chiou et al. (1995)[a] (SW Taiwan)	<50	3.85	48.13	1	5/611.99	5/611.99	616.99	616.99
	50–70		115.50	2.10 (0.70–6.80)	7/542.44	7.52/582.74	549.44	590.26
	>70		202.13	2.70 (0.70–10.20)	7/530.17	3.75/284.02	537.17	287.77

[a]Number of subjects estimated from person–years at risk.

we have

$$\frac{\mathrm{N}_i^e}{\mathrm{N}_i^r} = \frac{\mathrm{RR}_i^e}{\mathrm{RR}_i^r}. \tag{8}$$

With the joint assumption over T_i^e terms, we find that

$$N_i^e = \frac{1}{2} \cdot \left(\left\{ \mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{L}} - \frac{1}{A_0^r} \right\}^{-1} + \left\{ \mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{U}} - \frac{1}{A_0^r} \right\}^{-1} \right) \cdot \left(\frac{A_i^r}{N_i^r} \right)^{-1}. \tag{9}$$

Furthermore, we have $N_0^e = N_0^r$, in accordance with the invariant features exhibited by the referent group.

Cumulative incidence cohort studies: In line with what previously assumed with incidence rate cohort studies, we initially set $A_0^e = A_0^r$ and $N_0^e = N_0^r$, as these are the terms now entering the computation of RR_i measures via Equation (3). Both terms also appear in Equation (4), so in this case, it is straightforward to compute A_i^e and N_i^e terms. Recalling Equations (5) and (6) (as they keep unchanged for cumulative incidence cohort studies), we can write:

$$A_i^e = \frac{1}{2} \cdot \left\{ \frac{1 - \left(\mathrm{RR}_i^r \cdot \frac{A_0^r}{N_0^r} \right)}{\mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{L}} + \frac{1}{N_0^r} - \frac{1}{A_0^r}} + \frac{1 - \left(\mathrm{RR}_i^r \cdot \frac{A_0^r}{N_0^r} \right)}{\mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{U}} + \frac{1}{N_0^r} - \frac{1}{A_0^r}} \right\}, \tag{10}$$

$$N_i^e = -\frac{1}{2} \cdot \left\{ \frac{1 - \left(\mathrm{RR}_i^r \cdot \frac{A_0^r}{N_0^r} \right)^{-1}}{\mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{L}} + \frac{1}{N_0^r} - \frac{1}{A_0^r}} + \frac{1 - \left(\mathrm{RR}_i^r \cdot \frac{A_0^r}{N_0^r} \right)^{-1}}{\mathrm{SE}^2\left[\log\left(\mathrm{RR}_i\right)\right]_{\mathrm{U}} + \frac{1}{N_0^r} - \frac{1}{A_0^r}} \right\}. \tag{11}$$

Eventually, on a similar manner to that one implemented for N_i^e terms in incidence rate cohort studies, we can derive effective person–time terms via the following linear projection:

$$\frac{T_i^e}{T_i^r} = \frac{\mathrm{RR}_i^e}{\mathrm{RR}_i^r}. \tag{12}$$

We further omit the explicit computation of T_i^e for space constraints.

Bayesian benchmark dose modeling for dichotomous data: In this case, we couple the Allen et al. (2020b) "effective counts" method with the dichotomous case of the Shao and Shapiro (2018) model. The latter computes the BMDs by estimating the following quantity:

$$\log\left[P\left(\text{data}|\theta\right)\right] = \sum_{i=0}^{G-1}\left\{\log\binom{n_i}{y_i} + y_i \log\left[f\left(d_i|\theta\right)\right] + (n_i - y_i)\log\left[1 - f\left(d_i|\theta\right)\right]\right\}, \quad (13)$$

where θ represents the parameters that define a dose–response curve $f(d_i|\theta)$ (for our comparison purposes, we will focus on the Quantal-Linear and Dichotomous Hill models), d_i represents the dose level; n_i is the number of subjects in each dose group (i.e., N_i^e), and y_i is the number of subjects showing response in the corresponding dose group (i.e., A_i^e). Differently from its original version, the summation index is defined from $i = 0$ to $i = G - 1$ as the referent group is here marked by having $i = 0$. Equation (13) is the log-transformed likelihood function and serves as the foundation for the MCMC algorithms to estimate the parameters in the dichotomous dose–response models.

With respect to input data, to incorporate the "effective counts" treatment in a dichotomous model, it appears natural to set $n_i = N_i^e$ and $y_i = A_i^e$. However, it is must be noted that the n_i and y_i terms might not be anymore integers, after having undergone such a transformation. Therefore, for the binomial coefficient term appearing in the previous formula, we consider a classical extension to two real valued arguments through the Gamma function (for instance, see Winkelmann (2008), Díaz and Cano (2019)).

2.3.2 | Model epidemiological data as continuous data

Another possible way to model epidemiological dose–response data in a typical BMD modeling framework is to model the RR as a continuous response. Four quantities are required as input data when performing a BMD modeling using continuous data, that is, dose/exposure level, number of subjects, the mean value and standard deviation of the response. A point estimate of exposure for a number of exposure groups might be reported in the study, or the method described in Section 2.3.3 can be used to derive a reasonable point estimate for each exposure group if the exposure was reported in ranges. The sample size of subjects in each exposure group is typically reported in epidemiological studies. Then, we need to express the RR as mean and standard deviation (or its equivalents) to facilitate the BMD modeling as continuous data. Usually, epidemiological studies report the median, lower, and upper bound of the RR, and the confidence interval is skewed to the upper end. So, it is reasonable to assume that RR at each exposure level follows a lognormal distribution, and this distribution can be characterized by two parameters, $\bar{y}_i = \log(\text{RR}_i^e)$ (i.e., the logarithm of the median RR) and s_i' (i.e., the standard deviation of RR on a log scale). Depending on the reported confidence interval of RR reported, the s_i' can be calculated as $(2 \cdot Z_{0.975})^{-1} \cdot \log(\text{RR}_i^{\text{U}}/\text{RR}_i^{\text{L}})$ for 95th percentile CI or $s_i' = (2 \cdot Z_{0.95})^{-1} \cdot \log(\text{RR}_i^{\text{U}}/\text{RR}_i^{\text{L}})$ for 90th percentile CI. Then, as described in Shao et al. (2021), these four required quantities will be used in the following log-likelihood function to estimate the parameters of a dose–response model:

$$\log\left[P\left(\text{data}|\theta\right)\right] = -\frac{\text{N}}{2}\log\left(2\pi\right) - \sum_{i=0}^{G-1}\left(\frac{n_i}{2}\log\left(\gamma^2\right) + \frac{n_i\left\{\bar{y}_i' - \log[f(d_i|\theta)]\right\}^2 + (n_i - 1)\,s_i'^2}{2\gamma^2}\right), \quad (14)$$

where d_i is the exposure level at each group, n_i is the number of subjects in each group, $\bar{y}_i'$ is the log-transformed mean value of RR in each group, s_i' is the log-transformed standard deviation of RR in each group, N is the total number of subjects, and $G - 1$ is the number of dose groups. $f(d_i|\theta)$ represents a dose–response model with a vector of parameters θ. Given the settings expressed in the log-likelihood function above, we assume that the mean response of RR on the log-scale is represented by a chosen dose–response model, and the within-dose-group standard deviation, γ, is a constant across the exposure groups. In this study, for the purpose of comparison, one simple dose–response model, the Linear model, and one complex model, the Hill model as described in Shao and Shapiro (2018) is used for BMD estimation. Equation (14) is used as the key component in the MCMC model fitting process for parameter estimation. Parameters θ may vary from model to model depending on the model format.

2.3.3 | Adjusted exposure midpoint computations

Exposure groups are defined by clustering dose levels by intervals or medians. To ease comparisons among different epidemiological studies tackling diverse populations, adjustment to the exposure has to be taken into account as well. In one example reported by Tsuji et al. (2019), Lynch et al. (2017) estimated midpoint arsenic water exposure concentrations of the dose groups, adjusted to account for differences in water consumption rates and body weight in some foreign populations as compared to the United States. To estimate midpoint exposures for open-ended lowest or highest dose groups presented as less than or greater than a value, Lynch et al. (2017) assumed the midpoint between 0 and the lowest value or the midpoint between the highest value and two

times the highest value, respectively. We can formalize this approach in the following way. For dose intervals data type, shall δ_i^* and $\delta_i^\diamond$, respectively, represent the supremum and infimum (shortly, *sup* and *inf*) of a given dose interval referring to the *i*th group. Adjustment is done, assuming a certain water intake rate ω (measured in L/day) and an average water intake rate $\hat{\omega}$ that works out as a baseline and is usually taken equal to 2 L/day to account for US standards. In the case of open lower and upper intervals, we have

$$d_i = \begin{cases} \frac{1}{2} \cdot \delta_0 \cdot \left(\frac{\omega}{\hat{\omega}}\right) & \text{for } i = 0 \\ \frac{1}{2} \cdot (\delta_i^* + \delta_i^\diamond) \cdot \left(\frac{\omega}{\hat{\omega}}\right) & \text{for } i \neq 0 \ \wedge \ i \neq G-1 \\ \frac{3}{2} \cdot \delta_{G-1} \cdot \left(\frac{\omega}{\hat{\omega}}\right) & \text{for } i = G-1 \end{cases}. \quad (15)$$

Should no open interval be present, the middle formula $d_i = 2^{-1} \cdot (\delta_i^* + \delta_i^\diamond) \cdot (\omega/\hat{\omega})$ can serve for all dose groups. Eventually, in the case of epidemiological studies reporting medians instead of intervals, the above formula can be compacted to $d_i = \bar{\delta}_i \cdot (\omega/\hat{\omega})$, where $\bar{\delta}_i$ represents the median dose of a given exposure group.

2.3.4 | Definitions of benchmark response

To better compare these two modeling methods regarding BMD estimation, we need to carefully define equivalent BMRs for the dichotomous and continuous data, so that the impact on the BMD estimates from the BMR definition can be minimized. Unlike toxicological studies where the control group (i.e., exposure level is zero) is chosen as the reference group for BMD estimation, for epidemiological studies, the lower exposure group (rather than the zero-exposure group) is more appropriate to be selected as the reference group. To define equivalent BMRs for these two types of data, our strategy is to first set the BMR for dichotomous data and then calculate the corresponding BMR for continuous data.

For dichotomous data, we set the extra risk-based BMR at low (0.01%), medium (0.05%), and high (0.1%) three levels. The reason to use small BMR is that the response rates in the epidemiological studies are relatively small, for example, the response rate of bladder cancer in Chen et al. (2010a) ranges from 0.22% to 1.6%. Accordingly, the BMD can be calculated based on the following equation:

$$\text{BMR}_\text{D} = \frac{f(\text{BMD}) - f(ref)}{1 - f(ref)}, \quad (16)$$

where $f(\text{BMD})$ and $f(ref)$ represent the incidence rate at the BMD exposure level and reference exposure level, respectively, and $f(\cdot)$ is a dose–response model for dichotomous data. The numerator $f(\text{BMD}) - f(ref)$ calculates the difference in risk between the BMD exposed and background exposed groups. The denominator $1 - f(ref)$ represents the complement of the risk in the background exposed group and serves as a scaling factor to express the additional risk as a proportion or ratio relative to the complement of the risk in the background exposed group. By dividing the difference in risk (numerator) by the complement of the risk in the background exposed group (denominator), we obtain the extra risk ratio. This formula essentially measures the excess risk attributable to the BMD exposure under consideration.

For continuous data, we define BMR based on the relative change in central tendency of the response (i.e., RR in this case) to calculate the BMD. The following equation can be expressed as

$$\text{BMR}_\text{C} = \frac{g(\text{BMD}) - g(ref)}{g(ref)}, \quad (17)$$

where $g(\text{BMD})$ and $g(ref)$ are the RR at the BMD exposure level and reference exposure level, respectively, and $g(\cdot)$ is a dose–response model for continuous data. Similar to the extra risk formula employed for dichotomous data, the numerator $g(\text{BMD}) - g(ref)$ calculates the difference in risk between the BMD exposed and background exposed groups. However, in this case, the denominator $g(ref)$ represents the risk in the background exposed group, serving as the reference point. The formula expresses the change in risk relative to the baseline level, providing a measure of the relative increase in risk associated with the BMD exposure.

When we calculate the equivalent BMR_C, we assume that the incidence rate at the BMD level in the scenario of dichotomous data is equal to the incidence rate at the BMD level in the scenario of continuous data, that is, $g(\text{BMD}) = f(\text{BMD})/f(ref)$. Additionally, because the conversion from BMR_D to the equivalent BMR_C should be completed before the model fitting and BMD estimation, we need to directly use the input data for dose–response modeling, that is, $f(ref)$ is the incidence rate calculated by the effective counts of cases and total subjects, and $g(ref)$ is 1. As the previous formulas capture different aspects of risk assessment and provide measures of the additional risk or relative change associated with the BMD exposure, we use the following equation to calculate the BMR for continuous data that is equivalent to the defined BMR in dichotomous data:

$$\text{BMR}_\text{C} + 1 = \frac{f(\text{BMD})}{f(ref)} = \frac{\text{BMR}_\text{D} \cdot (1 - f(ref)) + f(ref)}{f(ref)}. \quad (18)$$

Using Chen et al. (2010a) as an example, there are 5 and 2283 effective counts of cases and non-cases, respectively, indicating $f(ref) = 5/2288$, so BMR_C is approximately 5% when $\text{BMR}_\text{D} = 0.01\%$. Therefore, the conversion should be conducted for each combination of epidemiological datasets and BMR_D values.

3 | RESULTS

In this section, we outline the main results of our analysis by the following three points: (1) refined input data as obtained by the data pretreatment, that is, computation of effective

counts and of adjusted exposure midpoints; (2) BMDs computed via the Bayesian BMD analysis, according to the continuous and dichotomous models; and (3) comparison of the previous models outcomes.

Regarding the first point, for all considered prospective cohort studies, in Tables 2 (bladder cancer data) and 3 (lung cancer data), we compute the effective number of cases (column 6b) and of subjects (column 7b), and we derive as well the adjusted exposure midpoints (column 4), basing our computation on the methods previously described, processing the raw data as shown in columns 1, 2, 5, 6a, and 6b. The water intake rate (column 3)—necessary to compute the adjusted exposure midpoints—was taken in agreement with Tsuji et al. (2019) and Lynch et al. (2017) who set 2.75 L/day as default assumption for Taiwan further multiplied by a 70/50 kg scalar factor to adjust for smaller body weight. Furthermore, as detailed in the tables captions, in a restricted number of cases, data were adapted to fit our computation; namely, the number of subjects was derived from person–years at risk only if this information was not originally present in the single prospective cohort study. In doing so, we employed the cohort number size and repurposed it according to the distribution of the person–time data per group, following in that case a cautious approach based on a uniform distribution assumption. In one case, we made use of a mortality study providing hazard ratios instead of RRs, while considering the limitations pointed out by Stare and Maucort-Boulch (2016) in employing the former measure at the place of the latter.

For the second point, with the data now presented in Tables 2 and 3, we perform a Bayesian BMD analysis using the continuous and dichotomous data models outlined in the previous section. The Bayesian BMD modeling and analyses were programed and completed in the R program. A more user-friendly modeling platform for epidemiological BMD modeling using the continuous data method described in the present study has been implemented in the online BBMD modeling system (Shao & Shapiro, 2018). For both modeling methods, we employ one simple model and one complex model for BMD estimation, that is, for the dichotomous data: Quantal-Linear and Dichotomous-Hill models; and for the continuous data: Linear and Hill models. As described in Section 2.3.4, we set the BMR at 0.01%, 0.05%, and 0.1% for all datasets when the dichotomous data modeling approach is applied, and the corresponding BMDs for continuous data are calculated. This latter information together with the entire results of the Bayesian BMD analysis are reported in the Supporting Information. To ease the comparison between the continuous and dichotomous models outcomes, we present the results of the BMD analysis, that is, the BMRs and their lower and upper bounds for a restriction to Quantal-Linear versus Linear model and Dichotomous-Hill versus Hill model in the scatterplots reported for each prospective cohort study in Figures 3a and 4a.

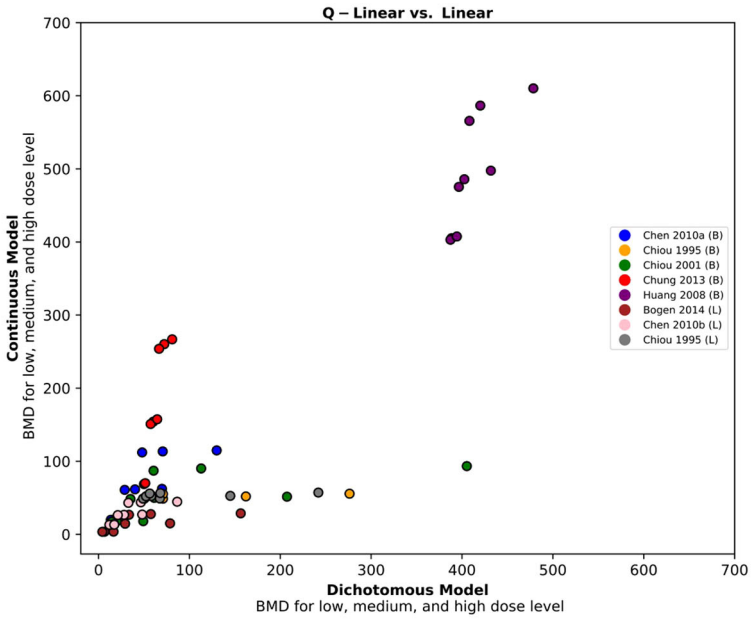
Eventually, regarding the third point, to compare the performances of the dichotomous and continuous models, we first compare the corresponding BMD estimates (including the median, lower, and upper bound) obtained from these two modeling approaches using a same dataset by calculating the correlation coefficient. These BMD estimates are visualized in Figures 3a and 4a for the simple model (with $r = 0.849$) and complex model (with $r = 0.554$) scenarios, respectively. We then employ two standard measures of rank correlation, that is, Kendall's $\tau - b$ coefficient and Spearman's ρ, quantifying the statistical nonindependence between the rankings of two variables over the same dose–response models, namely, Linear and Hill models. Both measures may take values spanning from -1 to 1; in particular, positive values assess how well the relationship between two variables can be described using an increasing monotonic function (Spearman's ρ) and how well a direct ordinal association between two measured quantities can be established (Kendall's $\tau - b$). We picture the results of such analysis in Figures 3b and 4b. As shown in these figures, we found comparable results with an average Spearman's rank correlation coefficient accounting to 0.939 ± 0.037 (computed via Fisher's Z transformation) and an average Kendall rank correlation coefficient equal to 0.861 ± 0.062.

4 | DISCUSSION

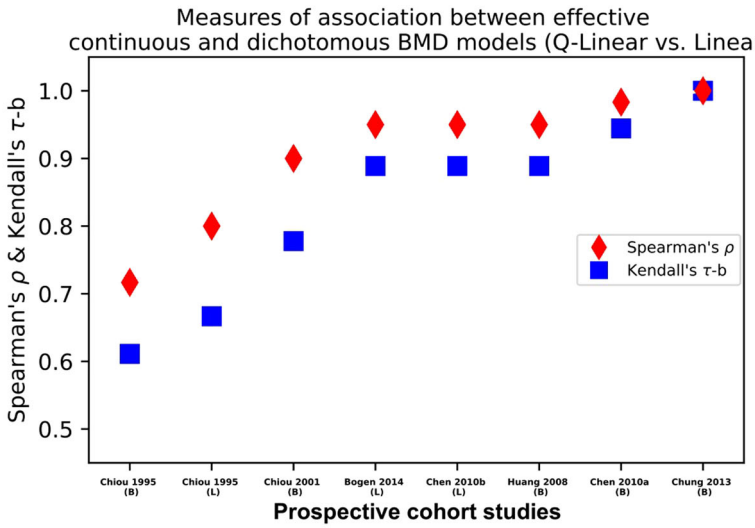
In this study, with the purpose of identifying a generalizable and standardizable BMD modeling method for typical epidemiological data published in the literature, two modeling strategies were deliberated and compared, that is, modeling the epidemiological data as dichotomous and continuous data, respectively, after careful data preprocessing. When modeling epidemiological data as dichotomous dose–response data, we utilize the commonly reported information (e.g., adjusted RR) in published studies to convert the raw counts of cases and non-cases to "effective counts" that essentially indicate the incidence only caused by exposure to the study chemical. In this case, the effective counts not only reflect the weight of each exposure group but also take the influence on the incidence rate from confounders into account. On the other hand, when modeling epidemiological data as continuous dose–response data, we treat the commonly reported adjusted RRs (with respect to important confounders) as continuous response and convert them to the format of mean and standard deviation. The adjusted RRs and sample size of subjects in each exposure show how health effects can be impacted by the exposure with respect to the reference group. It is important to note that the modeling methods we discussed in the study do not directly analyze raw epidemiological data but utilize the published data after appropriate processing and adjustment. We also want to mention that, to demonstrate the proposed methodology, we employed epidemiological cancer endpoint as an example, but it does not mean that this BMD modeling method can only be used by cancer effect. Additionally, whether the derived epidemiological BMD should be further extrapolated to a lower dose or how to perform the low-dose extrapolation for epidemiological BMD is out of the scope of the present study.

The adjustment and conversion of the published epidemiological dose–response data make them consistent with standardized data format used as input in BMD analysis. Con-

FIGURE 3 Comparison of dichotomous and continuous data models via Quantal-Linear and Linear dose–response models. Panel (a): Benchmark doses (BMDs) and their lower and upper bounds computed via dichotomous and continuous data models. Panel (b): Measures of associations of the latter models.

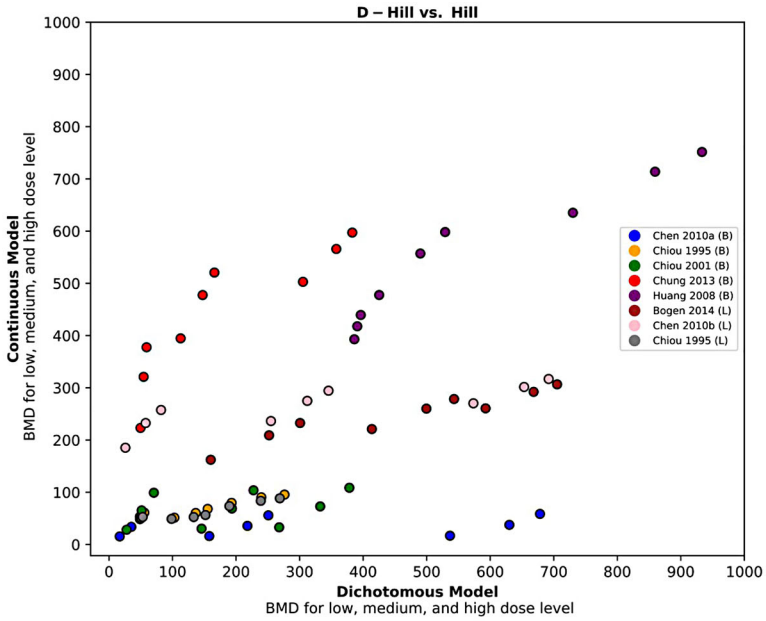


(a) Scatter plot of computed BMDs and their upper and lower bounds at different dose levels for the dichotomous (X-axis) and continuous (Y-axis) data models. Data coming from different prospective cohort studies (see right legend) align with a strong positive correlation ($r = 0.849$).

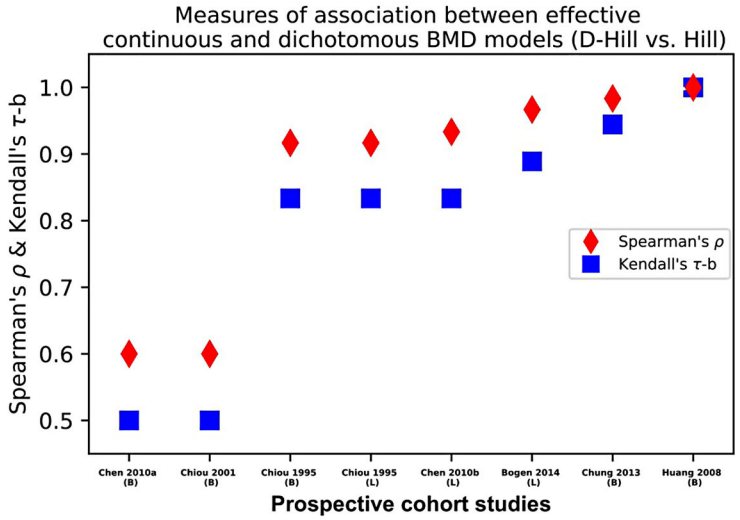


(b) Spearman's ρ and Kendall's τ-b measures of association for the dichotomous and continuous data models. On the X-axis, we report the prospective cohort studies which analyzed data belong to. On the Y-axis, we plot Spearman's ρ and Kendall's τ-b measures. Data are ordered according to the latter measures. Strong association between the two models is shown by almost all studies.

sequently, commonly used empirical dose–response models, as well as typical BMR definitions and settings, can be employed smoothly in the epidemiological BMD analysis. Because the focus of the comparison is the data structure for BMD estimation (dichotomous vs. continuous data), we took a number of strategies to mitigate the disturbance caused by other factors on the BMD estimates: (1) choosing comparable dose–response models for these two data types, that is, Quantal-Linear versus Linear model and Dichotomous-Hill versus Hill model; (2) equivalent BMR values for continuous data were calculated based on the specified BMR values for dichotomous data based on incidence rate and incidence rate the reference group. Although the format of exposure level is another key difference between epidemiological and toxicological studies, the same adjusted midpoint of exposure used in both types of data will not cause additional difference. The corresponding BMD, BMDL, and BMDU values estimated from these two types of data were analyzed for correlation; the correlation coefficients of 0.849 and 0.554 for the situations of simple and complex dose–response models, respectively, indicate that the BMD estimates from these two modeling methods are relatively consistent. The lower correlation coefficient generated in the situation of complex model may be caused by larger estimation uncertainty in model fitting. The compatible BMD estimates from the two methods are also justified by Kendall's $\tau - b$ and Spearman's ρ coefficients.



(a) Scatter plot of computed BMDs and their upper and lower bounds at different dose levels for the dichotomous (X-axis) and continuous (Y-axis) data models. Data coming from different prospective cohort studies (see right legend) align with a moderate positive correlation ($r = 0.554$).



(b) Spearman's ρ and Kendall's τ-b measures of association for the dichotomous and continuous data models. On the X-axis, we report the prospective cohort studies which analyzed data belong to. On the Y-axis, we plot Spearman's ρ and Kendall's τ-b measures. Data are ordered according to the latter measures. As for the Quantal-Linear and Linear dose-response models, also for the Dichotomous Hill and Hill models a strong association is observed in almost all studies.

FIGURE 4 Comparison of dichotomous and continuous data models via Dichotomous Hill and Hill dose–response models. Panel (a): Benchmark doses (BMDs) and their lower and upper bounds computed via dichotomous and continuous data models. Panel (b): Measures of associations of the latter models.

From a theoretical perspective, modeling the epidemiological data as dichotomous data and as continuous data for BMD estimation is fairly consistent. However, from a practical perspective, modeling RR as continuous response is a more favorable solution, because converting confidence interval to mean and standard deviation is much more convenient than using numerical methods to derive effective counts. Consequently, modeling RR as continuous data for BMD estimation is easier to be implemented in BMD modeling tools.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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