参考資料４
（第 24 回 WG 資料）

疫学研究データに BMD 法を適用する際の BMR の設定についての既存情報

１．はじめに

疫学研究データに BMD 法を適用する際の考え方や手順等のうち BMR の設定について検討するにあたり、日本及び欧米におけるガイダンス等の記載及び疫学研究データに BMD 法を適用した評価事例等を整理した。

２．ガイダンス等の記載状況

（１）「新たな時代に対応した評価技術の検討～BMD 法の更なる活用に向けて～」（2018 年７月評価技術企画ワーキンググループ）

本 WG で取りまとめた「新たな時代に対応した評価技術の検討～BMD 法の更なる活用に向けて～」において、疫学研究データに BMD 法を適用する際の論点の一つとして、BMR の設定が挙げられている。

（２）Update: use of the benchmark dose approach in risk assessment （EFSA, 2017）

疫学研究データについては、現在の GD の適用外としており、疫学研究に特化した GD が必要とされている（改訂案でもこの点は変わらない。）。

（３）Benchmark Dose Technical Guidance（U.S. EPA, 2012）

疫学研究については、動物実験ほど標準化されていないため、BMD 法の適用は個々に判断されるとしている。

BMR の設定については、疫学研究データ（二値データ）での 10%の BMR は、上方への外挿につながるため、しばしば１％の BMR が使用されることが記載されている。

（４）EHC239（IPCS, 2009）

疫学に特化した記載ではないが、BMR の選択には、技術的な側面と政策的な側面があることが述べられている。

また、二値データに対しては、通常バックグラウンドを補正する方法で表わされ、過剰リスク、追加リスク、相対リスクの３種類があること、連続値データには平均反応レベルの変化量で直接的に、または臨界値を上回る（下回る）試験動物の割合で間接的に示すことができることが述べられている。

（５）EHC240（IPCS, 2020）

動物試験と比較し、ヒトでの観察研究の対照群のばらつきが大きいことは、動物試験で適用されるBMRが必ずしも適用可能でないことを意味すること、ヒトの研究で使用されるBMRは、臨床的観点から正常であるか否かあるいは公衆衛生の観点から許容できるか否かに基づくべきであることが記載されている。

３．疫学研究データにBMD法を適用した評価事例（令和２年度調査事業報告書より）

（１）二値データを対象とした場合のBMRの設定

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
4	Bailer, A J et al.	1997	Estimating benchmark concentrations and other noncancer endpoints in epidemiology studies	coal mine dust	forced expiratory volume in one second (FEV_1)	8,146	過剰リスク、追加リスク	0.1%、1%、2%、10%	―
25	ATSDR	2012	TOXICOLOGICAL PROFILE FOR CADMIUM	cadmium	Low molecular weight proteinuriatt-Effect biomarker: human complex forming glycoprotein:pHC, β2-microglobulin: β2M	15,743	過剰リスク	10%	―
26	ATSDR	2012	TOXICOLOGICAL PROFILE FOR MANGANESE	manganese	score in the eye-hand coordination test	193	過剰リスク	5%、10%	―

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
31	EFSA	2020	Update of the risk assessment of nickel in food and drinking water	nickel	systemic contact dermatitis (SCD, eczematous flame-up reactions in the skin) /clinically cutaneous reactions	86	過剰リスク	10%	EFSAのガイダンス（EFSA 2017、重要資料No.5）に基づく
32	EFSA	2018	SCIENTIFIC OPINION Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food	PFOA	increased prevalence of abnormal serum levels of ALT	47,092	記載なし	3%	ー

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
33	EFSA	2015	Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water	nickel	Systemic contact dermatitis elicited in Ni-sensitive humans after oral exposure seen as flare-up reactions, worsening of allergic reactions (e.g. hand eczema, body erythema)	94	過剰リスク	10%	EFSAのガイダンス（Use of the benchmark dose approach in risk assessment 2009）に基づく
36	EFSA	2010	Scientific Opinion on Lead in Food	lead	CKD (defined as a GFR below 60mL/1.73 m^2 body surface/min)	14,778	過剰リスク	10%	EFSAのガイダンス（Use of the benchmark dose approach in risk assessment 2009）に基づく

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
37	EFSA	2009	Scientific Opinion on Arsenic in Food	arsenic	bladder cancer	8,102	過剰リスク	1%	NRCの評価書（Arsenic in Drinking Water、2001）に基づく
37	EFSA	2009	Scientific Opinion on Arsenic in Food	arsenic	arsenic-induced skin lesions	12,334	記載なし	1%	CONTAMIパネルは、5%又は10%の過剰リスクを推定することも可能であるが、1%の過剰リスクは観察されたデータの範囲内であると結論し、1%の過剰リスクを用量反応モデルに用いることとした

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
37	EFSA	2009	Scientific Opinion on Arsenic in Food	arsenic	lung cancer	570	記載なし	1%	NRCの評価書（Arsenic in Drinking Water、2001）に基づく
40	EPA	2010	Fluoride: Dose-Response Analysis For Non-cancer Effects. Health and Ecological Criteria Division Office of Water	fluoride	severe dental fluorosis (severe enamel fluorosis)	5,854	過剰リスク	0.5%、1%、5%	ー

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
47	JECFA	2011	Safety evaluation of certain contaminants in food Prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) ARSENIC (addendum) (pages 153 - 316) WHO Food Additives Series: 63. FAO JECFA Monographs 8.	arsenic	urinary cancer	6,888	追加リスク	0.50%	ー

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
47	JECFA	2011	Safety evaluation of certain contaminants in food Prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) ARSENIC (addendum) (pages 153 - 316) WHO Food Additives Series: 63. FAO JECFA Monographs 8.	arsenic	lung cancer	6,888	追加リスク	0.50%	ー

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
47	JECFA	2011	Safety evaluation of certain contaminants in food Prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) ARSENIC (addendum) (pages 153 - 316) WHO Food Additives Series: 63. FAO JECFA Monographs 8.	arsenic	skin lesions	14,080	追加リスク	0.5%、5%	ー
55	Chen, Chu-Chih et al.	2019	A benchmark dose study of prenatal exposure to di(2-ethylhexyl) phthalate and behavioral problems in children	di (2-ethylhexyl) phthalate (DEHP)	child behavior checklist (CBCL) and IQ scores	122	記載なし	5%、10%	ー

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠
56	Nogawa, Kazuhiro et al.	2017	Threshold limit values of the cadmium concentration in rice in the development of itai-itai disease using benchmark dose analysis	cadmium	incidence of itai-itai disease and/or suspected disease	405	追加リスク	1%、2%	イタイイタイ病の発症率が低いため、BMRを1%、2%に設定

（２）連続値データ（個人）を対象とした場合のBMRの設定

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠	ハイブリッド法適用有無
27	ATSDR	2007	TOXICOLOGICAL PROFILE FOR BENZENE	benzene	Benzene-induced decreased B cell count	250	記載なし	0.25SD	0.25SDの値が、統計学的に有意な平均B細胞数の減少が観察された最低ばく露群の平均ばく露レベルよりも低いため	なし

重要資料 No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR 種類	BMR 値	BMR 値の設定根拠	ハイブリッド法適用有無
28	CDC/NIOSH	2016	Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione	Diacetyl and 2,3-Pentanedione	FEV1 and FEV1/FVC	719	記載なし	0.10%	ー	なし
29	NRC	2000	Toxicological effects of methylmercury	methylmercury	Neurodevelopmental effects	1,022	追加リスク	5%	公衆衛生をより保護するために BMR を 5%とした	あり
30	EFSA	2020	Risk to human health related to the presence of perfluoroalkyl substances in food	perfluoroalkyl substances	reduction in antibody titres (against diphtheria ,tetanus , influence type b (Hib))	101	記載なし	10%	反応の変動が大きいことを考慮し、BMR をデフォルトの 5%ではなく 10%に変更	なし

重要資料 No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR 種類	BMR 値	BMR 値の設定根拠	ハイブリッド法適用有無
34	EFSA	2012	Scientific Opinion on the risk for public health related to the presence of mercury and methylmercury in food	methylmercury	neurological functions	2,524	追加リスク	5%、10%	ー	なし
35	EFSA	2010	SCIENTIFIC / TECHNICAL REPORT submitted to EFSA An international pooled analysis for obtaining a benchmark dose for environmental lead exposure in children	lead	Full Scale IQ score	1,333	記載なし	1 IQ point	ー	なし

重要資料 No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR 種類	BMR 値	BMR 値の設定根拠	ハイブリッド法適用有無
36	EFSA	2010	Scientific Opinion on Lead in Food	lead	blood pressure, SBP (cardiovascular effects)	519	過剰リスク	1%	対象とした集団における SBP の年平均 1%の上昇が健康上の懸念と見なされたため（SBP の年平均 1%の上昇は、高血圧症の治療を受けた集団の割合を 3.1%増加させ、脳卒中又は心筋梗塞による年間死亡率をそれぞれ 2.6%、2.4%増加させると推定）	なし
36	EFSA	2010	Scientific Opinion on Lead in Food	lead	Full Scale IQ score (neurotoxicity in young children)	1,333	過剰リスク	1%	BMR=１%は 1IQ ポイントに対応しており、1IQ ポイントの低下が社会経済的状態とその生産性に影響	なし

重要資料 No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR 種類	BMR 値	BMR 値の設定根拠	ハイブリッド法適用有無
42	EPA	2001	Integrated Risk Information System (IRIS) Chemical Assessment Summary Methylmercury (MeHg); CASRN 22967-92-6	methylmercury	Developmental neuropsychological impairment	1,916	記載なし	5%	―	あり
43	EPA	2001	Water Quality Criterion for the Protection of Human Health: Methylmercury Chapter 4: Risk Assessment for Methylmercury	methylmercury	nervous system	1,099	記載なし	5%	NRC の評価書（NRC2000、重要資料 No.29）に基づく	あり
44	Budtz-Jørgensen, E et al.	1999	Benchmark modeling of the Faroese methylmercury data: Final report to U.S. EPA	methylmercury	Deficits in several domains of brain function	1,022	追加リスク	2%、5%、10%	BMD と BMR の関係を調べるために、10%の他に、2%、5%についても BMR とした	あり

重要資料 No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR 種類	BMR 値	BMR 値の設定根拠	ハイブリッド法適用有無
46	JECFA	2011	WHO Food Additives Series: 63. FAO JECFA Monographs 8. Perchlorate	perchlorate	50% inhibition of iodide uptake	37	ヨウ素取込みの 50%阻害を BMR として設定	50%	健康な成人から得られた過塩素酸塩への短期及び長期ばく露後のヒトの臨床データから、ヨウ素取込みの 50%阻害が、TSH 又は甲状腺ホルモンのレベルの変化とは関連しないことが示されたため	なし
49	JECFA	2007	WHO Food Additives Series: 58 Food contaminants, Methylmercury	methylmercury	neurodevelopment (brainstem auditory evoked potentials)	878	記載なし	5%	NRC の評価書（NRC 2000、重要資料 No.29）に基づく	あり
50	JECFA	2004	WHO Food Additives Series: 52 Methyl Mercury	methylmercury	fetal neurotoxicity	1,628	記載なし	2%、5%、10%	ー	あり

重要資料 No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR 種類	BMR 値	BMR 値の設定根拠	ハイブリッド法適用有無
53	Kubo, Keiko et al.	2017	Estimation of Benchmark Dose of Lifetime Cadmium Intake for Adverse Renal Effects Using Hybrid Approach in Inhabitants of an Environmentally Exposed River Basin in Japan	cadmium	renal dysfunction (Glucose, protein, aminonitrogen, metallothionein, and β2-microglobulin in urine)	3,178	追加リスク	5%	従来の研究の BMR 値を利用	あり
58	Budtz-Jørgensen, Esben et al.	2018	Application of benchmark analysis for mixed contaminant exposures: Mutual adjustment of perfluoroalkylate substances associated with immunotoxicity	perfluoroalkylate substances	immunotoxicity	853	記載なし	5%	EFSA の評価書（EFSA 2018、重要資料 No.32）に基づく	なし

（３）連続値データ（サマリー）を対象とした場合の BMR の設定

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR 種類	BMR 値	BMR 値の設定根拠	ハイブリッド法適用有無
32	EFSA	2018	SCIENTIFIC OPINION Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food	PFOA	increased serum cholesterol	46,294	記載なし	5%	ー	なし
32	EFSA	2018	SCIENTIFIC OPINION Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food	PFOA	decreased birth weight	1,400	記載なし	5%	ー	なし

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠	ハイブリッド法適用有無
32	EFSA	2018	SCIENTIFIC OPINION Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food	PFOS	increased serum cholesterol	46,294	記載なし	5%	－	なし
32	EFSA	2018	SCIENTIFIC OPINION Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food	PFOS	decreased birth weight	901	記載なし	5%	－	なし

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠	ハイブリッド法適用有無
32	EFSA	2018	SCIENTIFIC OPINION Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food	PFOS	decreased antibody response after vaccination	431	記載なし	5%	ー	なし
38	EFSA	2009	SCIENTIFIC OPINION Cadmium in food - Scientific opinion of the Panel on Contaminants in the Food Chain	cadmium	Tubular damage (urinary β-2-microglobulin (β2M))	30,000	過剰リスク	5%	ー	あり

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠	ハイブリッド法適用有無
39	EFSA	2009	TECHNICAL REPORT OF EFSA Meta-analysis of Dose-Effect Relationship of Cadmium for Benchmark Dose Evaluation	cadmium	β2-microglobulinuria（β2-MG) for renal effects	30,000	過剰リスク、追加リスク	5%、10%	―	あり
41	EPA	2002	TOXICOLOGICAL REVIEW OF BENZENE (NONCANCER EFFECTS) (CAS No. 71-43-2) In Support of Summary Information on the Integrated Risk Information System (IRIS)	benzene	Reduction in ALC (absolute lymphocyte count)	88	one standard deviation change from the control mean	one standard deviation change from the control mean	EPAのガイダンス（Benchmark Dose Technical Guidance Document、2000）に基づき、対照の平均からの１SDの変化をBMRとした	なし

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠	ハイブリッド法適用有無
52	Kullar, Savroop S et al.	2019	A benchmark concentration analysis for manganese in drinking water and IQ deficits in children	manganese	performance IQ scores	630	追加リスク	1%、2%、5%	従来の研究のBMR値を利用（NRC2000、重要資料No.29他）	なし
54	Lachenmeier, Dirk W et al.	2011	Epidemiology-based risk assessment using the benchmark dose/margin of exposure approach: the example of ethanol and liver cirrhosis	ethanol	liver cirrhosis morbidity and mortality	1,477,887	過剰リスク	1.5%	ー	なし

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠	ハイブリッド法適用有無
57	Wetterings, Peter J M et al.	2016	Derivation of the critical effect size/benchmark response for the dose-response analysis of the uptake of radioactive iodine in the human thyroid	radioactive iodine (RAIU)	the inhibition of thyroidal iodine uptake	100	記載なし	20%	本研究デザインでは、相対的なRAIUデータで20%未満の変化を観察できないため、BMR値を20%とした	なし
4 再掲	Bailer, A J et al.	1997	Estimating benchmark concentrations and other noncancer endpoints in epidemiology studies	coal mine dust	forced expiratory volume in one second (FEV1)	8,146	過剰リスク、追加リスク	0.1%、1%、2%、10%	ー	なし

重要資料No.	発行機関/著者	発行年	タイトル	ハザード	エンドポイント	研究対象者数	BMR種類	BMR値	BMR値の設定根拠	ハイブリッド法適用有無
25 再掲	ATSDR	2012	TOXICOLOGICAL PROFILE FOR CADMIUM	cadmium	Low molecular weight proteinuriatt-Effect biomarker: human complex forming glycoprotein:pHC , β2-microglobulin: β2M	15,743	過剰リスク	10%	ー	なし

（別紙）

各 GL 等の記載内容（抜粋）

（１）「新たな時代に対応した評価技術の検討～BMD 法の更なる活用に向けて～」
（平成 30 年７月評価技術企画ワーキンググループ決定）

Ⅳ．指針策定に向けて整理した論点
２．BMR の設定
（２）疫学研究データ

疫学研究で得られたデータに BMD 法を適用する場合、ヒトのデータであり、一般的には動物試験に比べて標本数が多いことに留意して BMR を検討する必要がある。

食品安全委員会は、2013 年に取りまとめた「食品中のヒ素」の食品健康影響評価において、BMR は「がんのような重大疾病の発症割合では厳しく（例えば 1%又は 5%）、非致死的な疾患ではそれほど厳しくなく（例えば 5%又は 10%）、IQ などの検査値は代替指標（surrogate marker）であることから、疾患あるいは健康度とのつながりが明確なものに限定し、臨床的に意味のある最小の差（minimal clinical important difference）に従うべき」としている。

WG は、個人における数値の変化と集団における数値の変化では、公衆衛生上の意味合いが異なる点も十分に考慮して BMR を議論すべきであるとの認識で一致した。

ヒ素の評価書（2013）における記載は、以下のとおり：

「疫学データに BMD 法を適用する場合、BMR は本来、対象者の種類や NOAEL/LOAEL との一致ではなく、社会的に許容できるリスク増加の上限によって決められるべきものであると考えられる。すなわち、「がんのような重大疾病の発症割合では厳しく（例えば 1％又は 5％）、非致死的な疾患ではそれほど厳しくなく（5％又は 10％）、IQ などの検査値は代理指標値（surrogate marker）であることから、疾患あるいは健康度とのつながりが明確なものに限定し、臨床的に意味のある最小の差（minimal clinical important difference）に従うべき」と考えられる。ただし、バックグラウンドにばらつきがあると考えられるため、1％増加のレベルは計算上出せたとしても、実質的には意味をもたない可能性もある。

また、ゼロ曝露がないなど外挿しなければならない場合は利用するモデルに大きく依存し、また、交絡因子の関与が大きい場合はそれを考慮しなければならないため、よほど量反応関係が論理的に確立しているものではない限り、計算は慎重でなくてはならない。

したがって、「本評価における BMR を、発がん影響については 1%、皮膚病変についてはがんほど致死的ではないことから 5%、生殖・発生については飲料水を介したヒ素曝露でみられた乳幼児死亡及び胎児死亡はヒ素曝露以外の要因により生ずる可能性を考慮して 5%」と判断した。」

（２）Update: use of the benchmark dose approach in risk assessment (EFSA, 2017)

2. Assessment

2.1. Introduction

This document addresses not only the analysis of dose-response data from experimental studies but also considers the application to data from observational epidemiological studies.

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2.3.3. Interpretation and properties of the NOAEL and the BMDL

（略）

For human (epidemiological) data, lower BMR values may be used because the observed response is often lower than 10% (see Section 2.5.2).

（略）

2.5.8. Epidemiological dose-response data

In principle, the BMD approach would also be applicable to human data. BMD analysis of human data will be the subject of a separate guidance document of the EFSA SC.

（３）Benchmark Dose Technical Guidance (U.S. EPA, 2012)

2.2. Selection of the Benchmark Response Level (BMR)

2.2.1. Quantal (Dichotomous) Data

(略)

In addition, for epidemiological data, response rates of 10% extra risk would often involve upward extrapolation, in which case it is desirable to use lower levels, and 1% extra risk is often used as a BMR.

(略)

In summary:

· An extra risk of 10% is recommended as a standard reporting level for quantal data, for the purposes of making comparisons across chemicals or endpoints. The 10% response level has customarily been used for comparisons because it is at or near the limit of sensitivity in most cancer bioassays and in noncancer bioassays of comparable size. Note that this level is not a default BMR for developing PODs or for other purposes.

· Biological considerations may warrant the use of a BMR of 5% or lower for some types of effects (e.g., frank effects), or a BMR greater than 10% (e.g., for early precursor effects) as the basis of a POD for a reference value.

· Sometimes, a BMR lower than 10% (based on biological considerations), falls within the observable range. From a statistical standpoint, most reproductive and developmental studies with nested study designs easily support a BMR of 5%. Similarly, a BMR of 1% has typically been used for quantal human data from epidemiology studies. In other cases, if one models below the observable range, one needs to be mindful that the degree of uncertainty in the estimates increases. In such cases, the BMD and BMDL can be compared for excessive divergence. In addition, model uncertainty increases below the range of data.

2.2.2. Continuous Data

For continuous data, there are various possibilities for selecting the BMR. Regardless of which option is used, it is recommended that the BMD (and BMDL) corresponding to a change in the mean response equal to one control SD from the control mean always be presented for comparison purposes. This value would serve as a standardized

basis for comparison, akin to the BMD corresponding to 10% extra risk for dichotomous data.

(略)

A one SD shift in the control mean corresponds to an extra risk of 10% for the proportion of individuals below the 1.4th percentile or above the 98.6th percentile of controls for normally distributed effects.8 (See Figure 3 for an illustration.) While a one SD change is the recommended BMR for comparisons across BMDs, this value may not always be suitable as a BMR for determining a POD. That is, a change of one SD in the control mean would be statistically significant in most studies with 10 or more animals per dose group, and the corresponding BMD would generally be interpreted as a LOAEL, depending, of course, on the biological significance of the outcome being measured. Thus, as previously discussed for quantal data, judgments about the biological and statistical characteristics of the data must be made. For example, for frank effects, a lower BMR may be warranted (e.g., 0.5 SD).

(略)

In summary:

- Preferred approach: If there is a minimal level of change in the endpoint that is generally considered to be biologically significant, then that amount of change can be used to define the BMR.
- If individual data are available and a decision can be made about which individual levels can be reasonably considered adverse, then the data can be implicitly dichotomized using the hybrid model or explicitly dichotomized based on that cutoff value, and the BMR can be set as above for quantal data. Note that implicit dichotomization is preferred over explicit dichotomization, because of the loss of information associated with the latter.
- In the absence of any other idea of what level of response to consider adverse, a change in the mean equal to one control SD (or lower, e.g., 0.5 SD, for more severe effects) from the control mean should be used.

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2.3.3. Selecting the Model

2.3.3.2. Experimental design

（略）

The inclusion of covariates on individuals is sometimes desirable when fitting dose response models. For example, litter size has often been included as a covariate in modeling laboratory animal data in developmental toxicity studies. Another example is in modeling epidemiology data when certain covariates (e.g., age, parity) are included that are expected to affect the outcome and might be correlated with exposure. If the covariate has an effect on the response, including it in a model may improve the precision of the overall estimate by accounting for variation that would otherwise end up in the residual variance. Any variable that is correlated (non-causally) with dose and which affects outcome should be considered as a covariate.

APPENDIX A. EXAMPLES

A.6. Human Data

Opportunities for modeling human toxicological data are limited, and the human studies are less standardized than studies of experimental animals; thus modeling of human data is done on a case-specific basis. （略）

（４）EHC239 PRINCIPLES FOR MODELLING DOSE-RESPONSE FOR THE RISK ASSESSMENT OF CHEMICALS (IPCS, 2009)

6.6 Benchmark dose and benchmark response selection

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The BMR is the response for which the BMD is to be calculated. There are both technical and policy aspects associated with selecting the BMR. The technical aspects have to do with just how the BMR is expressed; different types of end-points, such as quantal and continuous, require different treatments. Also, in somewhat more complicated situations, such as when covariates have been used in the modelling, the BMD depends on the BMR and possibly on the values of the covariates. Policy issues have to do with just how high or

low down the dose-response curve the BMR should be. This section discusses the technical issues surrounding the choice of BMR and some of the consequences that need to be considered in making the policy decision about where to set the BMR, but it does not directly address the choice of its particular value.

The way in which the BMR is expressed depends upon the kind of response variable being modelled. For end-points with two states (affected/not affected), the BMR is usually expressed in a way that adjusts for background. Two equations are common. One is that of added risk (AR):

$$BMR_{AR} = f(BMD) - f(0)$$

where fx represents the dose-response function evaluated at dose x. The other, which is probably most widely used, is extra risk (ER):

$$BMR_{ER} = \frac{f(BMD) - f(0)}{1 - f(0)}$$

where added risk is divided by the non-affected fraction of the nonexposed population. The response at the BMD_{ER} is always smaller than the response at the BMD_{AR} for the same numerical value of BMR when there is a background incidence. However, for small to moderate background response, the difference is small.
A third equation, common in epidemiological analyses, but applicable to animal studies as well, is relative risk (RR):

$$BMR_{RR} = f(BMD) / f(0)$$

BMRs for continuous end-points can be expressed directly in terms of changes in the mean response level or indirectly in terms of the fraction of experimental animals that exceed (or drop below) some critical level. For example, the BMD for mean adult body weight might be selected to be the dose at which the mean body weight drops below 90% of the body weight in controls or at which brain acetylcholinesterase activity is inhibited by 10% relative to control levels (this is often termed the critical effect size). One might also specify a fixed value or fixed drop in the mean,

selecting, for example, the dose at which the mean nerve conduction velocity drops below a fixed rate or a fixed difference from that in unexposed individuals. For end-points that demonstrate a sigmoidal response, as does enzyme induction, it has been suggested (Murrell et al., 1998; see Gaylor & Aylward, 2004, for a contrary argument) that a formulation similar to extra risk be used: for these end-points, the authors suggest that the BMD is best characterized as the dose at which the response is a specified fraction of the total dynamic range (e.g. the difference between background and maximum possible induction) of the response. The Gaylor & Aylward (2004) approach considers a certain setting within the definition of the response (i.e. a 1% change) and compares the uncertainties in the resulting BMD with the uncertainties in BMDs estimated using the specific setting in the "hybrid" approach. Thus, their conclusion may not hold in general terms (e.g. considering a 5% or 10% change in response relative to the total dynamic range).

Indirect or "hybrid" approaches have been advocated by Crump (2002) and Gaylor and his co-authors (Gaylor & Slikker, 1994; Kodell et al., 1995). In indirect approaches, the relationship between the mean of a continuous variable and dose is modelled, in the same manner as in the direct approaches. Next, a critical value for the continuous variable is determined that is to be considered as adverse, and an extra (or additional) risk BMR is selected for which to calculate a BMD. It is preferable that the critical value be based upon biological considerations, but it may otherwise be a value in the tail of the distribution of values in the control group. As the mean response increases, so will the fraction of subjects that exceed the previously determined critical value. The BMD is the dose at which the fraction exceeding the critical value corresponds to the fraction of affected animals associated with the BMR as defined for quantal data (e.g. BMR_{ER}).
It is possible to approximate the BMD as calculated in the previous paragraph (Crump, 1995) for a critical value corresponding to a "small" (e.g. 0.1-2%) risk in the control group and extra risk in the vicinity of 10%. This BMD corresponds approximately to the dose

at which the mean of the response variable differs from the control mean by an amount equal to the standard deviation of the control group. This gives another way to specify a BMR for continuous variables, based on the variability of the animals used in the bioassays.

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In some cases, the dose is not the only independent variable in a dose-response model. For example, in epidemiological studies, often many covariates that help characterize an individual and that might influence the response variable and be incidentally associated with the exposure variable are included in analyses in an attempt to reduce bias in the estimates of the effects of exposure (see section 6.2.1.4). In developmental bioassays, characteristics of the dam or the litter as a whole (e.g. number of implantation sites) may be used as a covariate in the modelling to help explain some of the additional variation among litters usually seen in such studies. Even adult-only rodent bioassays are usually segregated by sex. Typically, then, the assessor needs to decide for which values of the covariates BMDs need to be calculated. When there are few, discrete covariates, it may make sense to calculate a separate BMD for each set of values (e.g. a BMD for both males and females). When covariates are continuous (or treated as such, as in number of implantation sites), in an animal bioassay, it is usual to pick a typical value in the control group. However, if BMD changes with the value of the continuous variable, a detailed analysis of the dependency should be undertaken (e.g. modelling the BMD as a function of that covariate). If the variable makes sense for extrapolation to the human situation, it might be informative to calculate the BMDs for several values of the covariate, to evaluate the sensitivity of the BMD to the range of covariate values for humans.

（5）EHC240 Principles and methods for the risk assessment of chemicals in food (IPCS, 2020)

Although most of the methodology described in this chapter can in principle be applied to estimating the BMD and corresponding confidence interval using observational data from epidemiological studies, there are important methodological considerations that may require adaptations. These relate to the fact that DRM has, to a large extent, been designed around the use of data from controlled laboratory animal experiments. The types of information available from observational epidemiological studies often differ from the types of information derived from experimental animal studies.

For BMD modelling, the lack of a controlled experimental setting is the most important difference between observational studies and controlled experimental studies. The observational setting means that adjustment for several covariates is often needed when doing a BMD analysis. PROAST/EFSA BMD software does allow analysis of covariates. If the currently existing BMD software is not designed to deal with such multivariable modelling requirements, this is not problematic, as many existing statistical packages (STATA, SAS and R, to name a few) can be used for such purposes. Even if existing BMD software were to be updated to allow for the handling of several covariates, another issue is that access to individual participant data from human studies is severely restricted by data protection requirements - that is, sending or sharing individual participant data containing sensitive health and sociodemographic information is often not compatible with data protection regulations.

Although these are important concerns, the problem of data sharing can be overcome by modelling aggregated (or quantile) data. For that purpose, confounder-adjusted summary statistics that reflect the underlying dose-response curve must be generated. This can be done by dividing the exposure variable into enough quantiles (quartiles,

quintiles, deciles or finer subdivision) and then, using multivariable analyses, generating the expected confounder-adjusted response in each quantile using the lowest quantile of exposure as the point of comparison (Wheeler et al., 2017). Such an approach is compatible with how epidemiological data are frequently analysed and reported. The loss of information when using aggregated quantile data is generally considered non-substantial if the numbers of quantiles generated are sufficiently large to allow for proper evaluation of the underlying dose-response curve. The only specifications needed for such an approach are that, for each quantile, the authors report the response (e.g. mean response, proportional hazard or excess risk), its standard error, the number of subjects and the median exposure. For quantal outcomes where relative risk estimates are used, it is also important for authors to provide information that allows for the extraction of the absolute risk in each quantile. This approach is essentially comparable to how controlled animal experiments are analysed, where the use of summary statistics, not individual data, is accepted.

Another difference between modelling data from human observational studies and modelling data from experimental studies is the lack of a well-defined control group, or “zero dose”. For human observational studies, the equivalent of a zero dose would be the lowest quantile that is used as the point of comparison. The exposure level and the background response for that point depend on the number of quantiles generated to describe the dose-response curve. The exposure level for that point may also differ across study populations, which highlights the need to model more than one study, if possible, to establish whether consistent results can be obtained. Extrapolation beyond the observed data should generally not be done without clear justification.

In human observational studies, the exposure range is often narrower than that which can be created in experimental settings (i.e. laboratory animal studies often use much higher doses than those to which humans would normally be exposed); in contrast, the sample

size is usually much larger. A narrow exposure range has the implication that the full theoretical (e.g. sigmoidal) dose-response curve is often not observed. Instead, the dose-response curve depends on the level and range of exposure in the observed population, and it can be either nonlinear (at the two extremes of the sigmoidal curve) or approximately linear. The use of linear models can therefore in some cases be justified at the expense of using more complex nonlinear models. In such cases, the benefit of using BMD analyses is confined to determining the BMD and corresponding confidence intervals based on a predefined response that is considered biologically relevant (the BMR). Furthermore, the high variability in human observational studies, relative to the controlled settings in an experimental animal study, means that the same default BMR frequently applied in laboratory animal studies is not necessarily applicable. The BMR used in human settings should be based on what is considered normal or abnormal from a clinical point of view or acceptable or unacceptable from a public health point of view.