International Symposium on the Risk Assessment of Pesticides

US Process: Selection of Appropriate Endpoints for Setting Acute Reference Doses (ARfD)

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The opinions expressed are those of the speaker and do not represent the USEPA.

農薬のリスク評価に関する国際シンポジウム

米国のプロセス: 急性参照用量(ARfD)設定のための適切なエンドポイントの選定

コンサルタント
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米国環境保護庁としての公式な見解でなく
発表者の個人の見解である旨、ご了承ください

Topic: Overview of ARfD Setting

- History
- Exposure scenarios assessed
- How risk is expressed
- General comments about practice of setting ARfDs

トピックス：ARfD設定方法の概要

- 背景
- 評価対象とされるばく露シナリオ
- リスクをどのように表現するか
- ARfDの設定に関する一般的な考え方

Some Relevant History

- During the 1990s, pesticide re-registration was expanded to include acute dietary risk assessment.
- 1996 Food Quality Protection Act (FQPA)
  - Reasonable certainty of no harm to infants and children from aggregate exposure to a pesticide.
    - FQPA 10X Safety Factor
    - Cumulative Risk; http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides

主な歴史的背景

- 1990年代に、農薬の再登録の対象が食事を介した急性影響のリスク評価へと拡大
- 1996年　食品品質保護法（FQPA）の制定
  - 多様な経路による農薬の複合ばく露について
    乳幼児に影響がないことの合理的な保証として
    - FQPA　10×　安全係数
    - 累積リスク

http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides

Pesticide Exposure Scenarios Typically Assessed with ARfDs

One day dietary oral exposure for food and drinking water

FQPA: USEPA must consider risks from "aggregate" exposures to a pesticide when establishing the legally permitted level of a pesticide in a food.

Dietary	
Acute Oral (One Day)	
Chronic Oral (6 months - Lifetime)	
Residential	
Incidental Oral Short Term (up to 30 days)	
Incidental Oral Intermediate Term (1 to 6 months)	
Occupational/Residential	
Dermal	**Inhalation**
Short Term	Short Term
Intermediate Term	Intermediate Term
Long Term	Long Term

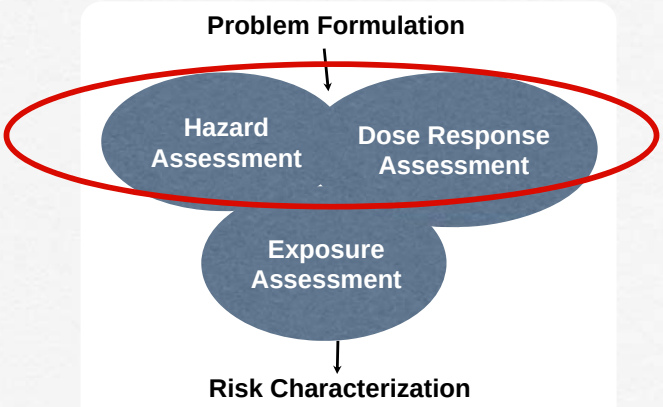
ARfD値を用いて評価する農薬ばく露の典型的シナリオ

食品と飲料水による1日の食事由来の経口ばく露量

FQPA: USEPAは、食品中の農薬にかかる法的許容量を決定する際に、農薬への「複合」ばく露のリスクを考慮しなければならない。

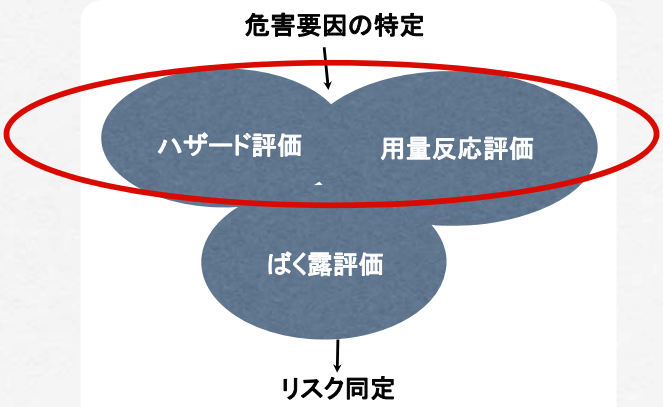
食事由来	
急性経口ばく露（1日）	
慢性経口ばく露（6か月～生涯）	
居住地由来	
偶発的な短期経口ばく露（30日以内）	
偶発的な中期経口ばく露（1～6か月）	
職業由来／居住地由来	
経皮	**吸入**
短期	短期
中期	中期
長期	長期

General Process for Setting ARfDs



- Population Groups
- Decision Process
- Uncertainty Factors

ARfD設定の一般的な手順



- 対象となる集団
- 決定プロセス
- 不確実係数

The US process is similar to JMPR and other agencies/organizations, but, there are a few differences.

- Gather and examine all data.
- Identify population groups for which toxicity values are necessary.
- Select critical effects and doses to match and evaluate acute exposure durations.
- Identify uncertainties and apply appropriate factors.
- Explain the reasoning behind the choices made and describe assumptions, uncertainties, data gaps.

米国のプロセスはJMPR(FAO/WHO合同残留農薬専門家会議)及び他の組織/機関と類似しているが、いくつかの違いがある

- 全てのデータを総合して検討
- 毒性値の設定が必要な集団を特定
- 決定的な影響と用量を選び、急性ばく露の期間を特定
- 不確実要素を特定し、適切な係数を適用
- なぜそのような選択がなされたかの説明と、仮定、不確実性及びデータギャップの記述

Process - Population Groups

US Population- Age groups that are assessed for exposure to pesticides:

All infants < 1 yr.
Children 1-2 yrs.
Children 3-5 yrs.
Children 6-12 yrs.
Youth 13-19 yrs.
Adults 20-49 yrs.
Adults 50+ yrs.
Females 13-49 yrs.

USEPA evaluates the need to establish ARfDs for two groups:

- Women of Childbearing Age (females 13-49 years)
- General Population including Infants & Children

JMPR - a single ARfD unless a developmental endpoint drives a conservative ARfD for the general population.

プロセス：対象となる集団の設定

農薬のばく露評価における米国国民の年齢別グループ

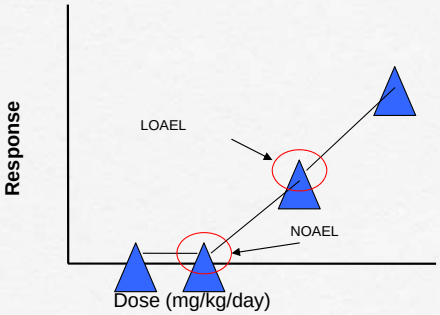
1歳未満の乳児
1～2歳の幼児
3～5歳の幼児
6～12歳の小児
13～19歳の若者
20～49歳の成人
50歳以上の成人
13～49歳の女性

USEPAは、2つのグループに対してARfDの設定が必要と判断

- 妊娠する可能性のある女性（13～49歳の女性）
- 乳幼児を含めた一般の集団

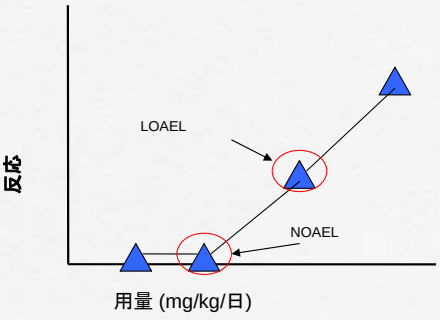
JMPRは：
発生毒性に由来するエンドポイントが、一般の集団に対してより保守的なARfDを導く可能性がなければ、全ての集団に対して単一のARfD を設定

Dose Response Assessment



- Select Point of Departures (PoDs) for critical effects (most sensitive endpoint of concern)
  - can be based on NOAELs, LOAELs (or modeled Benchmark Doses)
  - can be based on more than one endpoint or study
- When the chronic RfD (ADI) is higher than the ARfD, the chronic RfD is reconsidered

用量反応評価



- 決定的影響（懸念されるエンドポイントのうち、最も感受性の高い影響）に対する起点を選定
  - NOAEL、LOAEL（又は数理モデルにより算出されたBMD）に基づいてもよい
  - 2つ以上のエンドポイント又は試験に基づいてもよい
- 慢性のRfD（ADI）がARfDを上回る場合は、慢性のRfD（ADI）を再検討

ARfD NOAEL Cut Off

- USEPA pesticide program does not specify a cutoff per se, but in practice, ARfDs based on a NOAEL of 500 mg/kg bw/day or greater are not common.
- Effects seen at very high treatment doses or excessive doses, may not be appropriate to use as the basis of a NOAEL.

ARfD NOAEL のカットオフ値

- USEPA農薬プログラムは、カットオフ値そのものは特定しないが、通常NOAELが500 mg/kg体重/日又はそれ以上の場合ARfDは設定しない
- 非常に高い用量又は過剰な用量で見られた影響をNOAEL算出の根拠に用いることは適切ではない

ARfDs - Default Uncertainty/Safety Factors

- 1-10X for human inter-individual differences in sensitivity
- 1-10X for inter-species differences
- 1-10X for LOAEL to NOAEL extrapolation
- 1-10X for database uncertainties
- *Registered Pesticides: An additional “10X FQPA Safety Factor” is applied for infants and children, which can be removed or reduced based on data.

Pharmaco-kinetic/dynamic Modeling: http://www2.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos

Data Derived Extrapolation Factors:

2014 USEPA Guidance, http://www2.epa.gov/osa/guidance-applying-quantitative-data-develop-data-derived-extrapolation-factors-interspecies-and

Allometric Scaling (BW ¾): http://www2.epa.gov/osa/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

ARfD – 一般的な不確実係数/安全係数

- 1–10X ヒトの感受性の個人差に対して
- 1–10X 種差に対して
- 1–10X LOAELをNOAELに外挿することに対して
- 1–10X データベースの不確実性に対して
- *登録農薬: “10X FQPA 安全係数”が全ての乳幼児を対象として追加される。ただし、データに基づいて削除したり、小さくしたりすることが可能

薬物動態モデル http://www2.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos

外挿要因から得られるデータ

USEPAガイダンス（2014年） http://www2.epa.gov/osa/guidance-applying-quantitative-data-develop-data-derived-extrapolation-factors-interspecies-and

アロメトリースケール(BW ¾): http://www2.epa.gov/osa/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

How is Acute Dietary Risk Estimated?

Risk is a function of exposure, toxicity, susceptibility.

Residue (mg pesticide/kg food) X Consumption (kg food/kg bw/day)

$$\frac{\textbf{Exposure (mg/kg b/day)}}{\textbf{ARfD (or aPAD)}} \textbf{ X 10} = \textbf{\%ARfD (or aPAD)}$$

$$\text{ARfD (mg/kg bw/day)} = \frac{\text{NOAEL (mg/kg bw/day)}}{\text{Uncertainty factors}}$$

"Population Adjusted Dose" (aPAD) (mg/kg bw/day) is the ARfD with consideration of the FQPA 10X safety factor

食事由来の急性リスクの推定

リスクは、ばく露量、毒性、感受性の関数として計算される

ばく露量 (農薬mg/食品kg) × 摂取量 (食品kg/kg体重/日)

$$\frac{\text{ばく露量 (mg/kg体重/日)}}{\text{ARfD (又は aPAD)}} \times 10 = \textbf{\%ARfD (又は aPAD)}$$

$$\text{ARfD (mg/kg体重/日)} = \frac{\text{NOAEL (mg/kg体重/日)}}{\text{不確実係数}}$$

「母集団補正値」(aPAD) (mg/kg体重/日)は、10倍のFQPA安全係数を考慮した急性参照用量（ARfD）

Topic. Identifying Acute Hazards (Repeat Dose Studies)

- US Data Requirements
- Retrospective Analysis of ARfDs
- Case Examples (repeat dose studies)

トピック：急性のハザードの特定化（反復投与試験）

- 米国のデータ要求
- 急性参照用量（ARfD）の遡及的解析
- 事例（反復投与試験）

Toxicity Data Requirements for USEPA Pesticide Registration

Test Guideline Study	Food Use	Nonfood Use
Acute Oral – Rat	X	X
Acute Dermal	X	X
Acute Inhalation – Rat	X	X
Primary Eye Irritation – Rabbit	X	X
Primary Dermal Irritation – Rabbit	X	X
Dermal Sensitization	X	X
Acute Neurotoxicity – Rat	X	X
Delayed Neurotoxicity - Hen	CR	CR
90-Day Oral – Rodent (Rat/Mouse)	X	CR
90-Day Oral– Non Rodent (Dog)	X	CR
21/28-Day Dermal	X	NR
90-Day Dermal	CR	X
90-Day Inhalation – Rat		CR
90-Day Neurotoxicity - Rat	X	X

Test Guideline Study	Food Use	Nonfood Use
Chronic Oral- Rat	X	CR
Carcinogenicity - Mouse	X	CR
Carcinogenicity –Rat	X	CR
Prenatal Developmental – Rat	X	X
Prenatal Developmental – Rabbit	X	X
Reproduction & Fertility Effects	X	X
Developmental Neurotoxicity	CR	CR
Bacterial Reverse Mutation Assay	X	X
In Vivo Mammalian Cell Assay	X	X
In Vitro Cytogenetics	X	X
Metabolism & Pharmacokinetics	X	CR
Dermal Penetration	CR	CR
Immunotoxicity	X	X

X = Required; CR = Conditional Requirement

USEPA（米国環境保護庁）農薬登録に必要な毒性データ

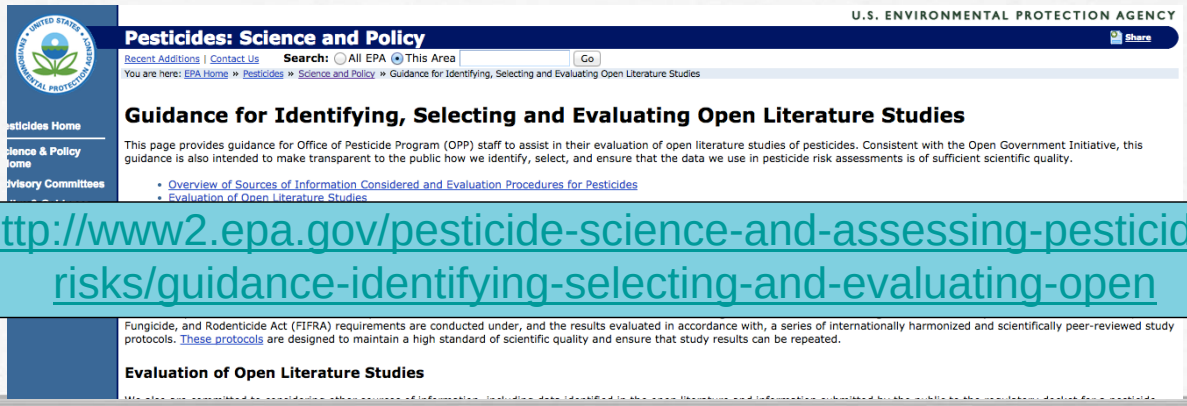
テストガイドラインに基づく試験項目	食用	非食用
急性経口毒性－ラット	X	X
急性経皮毒性	X	X
急性吸入毒性－ラット	X	X
眼刺激性－ウサギ	X	X
皮膚刺激性－ウサギ	X	X
皮膚感作性	X	X
急性神経毒性－ラット	X	X
遅発性神経毒性－ニワトリ	CR	CR
90日間経口毒性－げっ歯類（ラット/マウス）	X	CR
90日間経口毒性－非げっ歯類（イヌ）	X	CR
21/28日間経皮毒性	X	NR
90日間経皮毒性	CR	X
90日間吸入毒性－ラット		CR
90日間神経毒性－ラット	X	X

テストガイドラインに基づく試験項目	食用	非食用
慢性経口毒性－ラット	X	CR
発がん性－マウス	X	CR
発がん性－ラット	X	CR
発生毒性－ラット	X	X
発生毒性－ウサギ	X	X
繁殖能・生殖能への影響	X	X
発達神経毒性	CR	CR
復帰突然変異試験（微生物）	X	X
In vivo－動物細胞試験（ほ乳類）	X	X
In vitro－細胞毒性	X	X
代謝及び薬物動態	X	CR
皮膚透過性	CR	CR
免疫毒性	X	X

X = 必要; CR = 場合によっては

Other Sources of Data

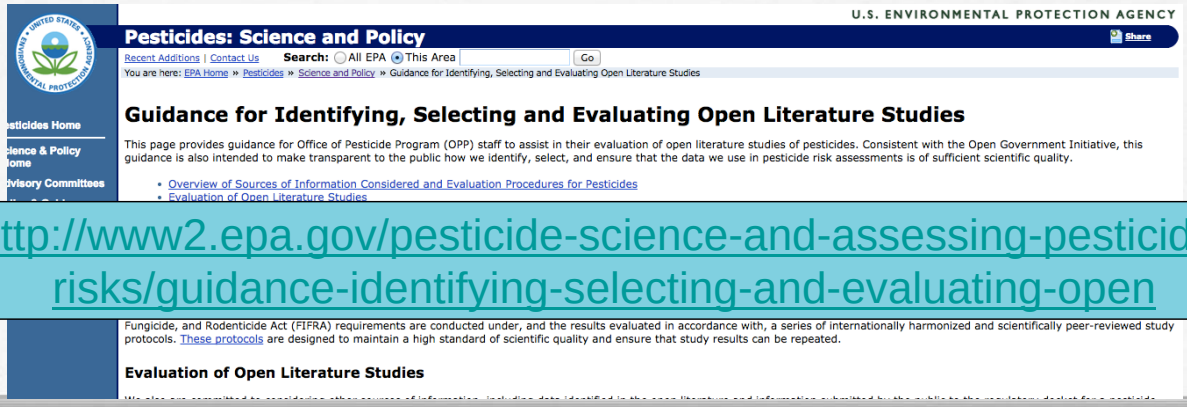
- USEPA Office of Pesticide Programs
  - “....considers multiple sources of information when conducting risk assessments for pesticides . . . studies that are the most relevant and informative to risk assessment are those that clearly and fully describe study design, conduct and methods, as well as providing access to the underlying data.”



http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-identifying-selecting-and-evaluating-open

他のデータソース

- USEPA 農薬プログラム事務局
  - “....農薬のリスク評価の実施に当たっては、複数の情報源からの情報を考慮する. . . リスク評価において、最も信頼でき情報に富む試験成績は、試験設計、実施及び試験方法が明確かつ全て記載され、その背景データが下記のサイトに公表されている試験である”



http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-identifying-selecting-and-evaluating-open

Principles of Requiring Data for Pesticides

- Insecticide, Fungicide, and Rodenticide Act (FIRFA) provides strong authority to require data and to issue “Data Call-ins”.
- 2013 Guiding principles found at http://www2.epa.gov/sites/production/files/2015-04/documents/data-require-guide-principle.pdf
  - Ensure sufficient information to support registration decisions that are protective of public health and the environment.
  - Focus on the most relevant information to the assessment.
  - Avoid generation of data that does not materially influence the scientific certainty of a regulatory decision and results in unnecessary use of time and resources, data generation costs, and animal testing.

農薬のデータ要求の原則

- 殺虫剤、殺菌剤、殺鼠剤条例（FIFRA)によりデータを要求し、“Data Call-ins”を公表する強い権限を与えている
- 2013 年の指針原則は以下のサイトにある http://www2.epa.gov/sites/production/files/2015-04/documents/data-require-guide-principle.pdf
  - 国民の健康と環境を保護するため、農薬登録の決定を支持する十分な情報を確実にすること
  - 評価に最も関わりのある情報に焦点が当てられていること
  - 措置の決定に必要な科学的確実性に実質的に影響しないデータの作成を避け、結果として、時間と人材、データ作成費用及び実験動物の浪費を避ける

Decision Process for Establishing an ARfD

Developmental effects (in utero)? — Yes → Establish ARfD for females 13-49 years.

↓ No

Acute neurotoxicity?

Maternal toxicity in developmental studies, or effects in other studies attributable to a single dose? — Yes → Establish ARfD for general population including infants and children.

No → ARfD not necessary.

ARfD設定に至るプロセス

発達影響（子宮内）？ — Yes → 13-49歳の女性に対してARfDを設定

↓ No

急性神経毒性？

発生毒性試験における母体毒性は？
又は他の試験で単回投与による影響は？ — Yes → 乳幼児を含む一般集団に対してARfDを設定する

No → ARfDの設定は不要

A Retrospective Analysis of the USEPA Pesticide Assessments

Science policy decisions made for ARfDs.

USEPAの農薬評価における遡及的解析

ARfD設定のための科学的な方針の決定

Human and Ecological Risk Assessment, 20: 1550–1564, 2014

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HAZARD ASSESSMENT ARTICLES

Setting Pesticide Reference Doses: A Retrospective Analysis Examining Key Data and Choices

Elizabeth Holman[1,2] and George Gray[2]
[1]Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, DC, USA; [2]Department of Environmental and Occupational Health, Center for Risk Science and Public Health, George Washington University, School of Public Health and Health Services, Washington, DC, USA

ABSTRACT

Toxicity tests are widely used to set "acceptable" levels of chemical exposure. Different organizations have identified a base set of tests specifying a mix of endpoints, durations, and species to be tested. A specific test and endpoint is chosen as the basis for calculation of human health risk values like reference doses (RfDs). This study empirically evaluates the data and choices made in setting acute and chronic RfDs for 352 conventional pesticides. The results suggest that for Acute, Acute-Female Specific, and Chronic RfDs one test is used far more than others. Ninety-six percent of the 116 Acute Female-Specific RfDs relied on a developmental toxicity test and 78% of Chronic RfDs used the chronic bioassay. Tests in rats were used far more often than other species in all RfD calculations. For all types of RfDs a total uncertainty factor of 100 was most common although values as low as 1 and as high as 3000 were seen. These results provide insights not only into the science policy frameworks used, but also into ways toxicity testing and risk assessment may be streamlined and made more efficient.

Key Words: risk assessment, reference dose, science policy, pesticides.

INTRODUCTION

Toxicity tests are widely used to set quantitative risk values used in safety assessment. The U.S. Environmental Protection Agency's (USEPA's) Office of Pesticide

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The opinions in the article are those of the authors and do not necessarily reflect policies of the USEPA or the U.S. government.
Address correspondence to Elizabeth Holman, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Ariel Rios Building, 1200 Pennsylvania Ave. NW, Mail Code 7509P, Washington, DC 20460, USA. E-mail: Holman.Elizabeth@epamail.epa.gov

Holman and Gray: Human and Ecological Risk Assessment, 20: 1550–1564, 2014

- Retrospective analysis for 352 Conventional Pesticides as of March 2013.
  - 24% Insecticides; 37% Herbicides; 22% Fungicides; 17% other.
  - 352 is not the exact number of registered pesticides but still is a reasonable database to look at trends (not absolute numbers/percentages).

e/terms-

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HAZARD ASSESSMENT ARTICLES

Setting Pesticide Reference Doses: A Retrospective Analysis Examining Key Data and Choices

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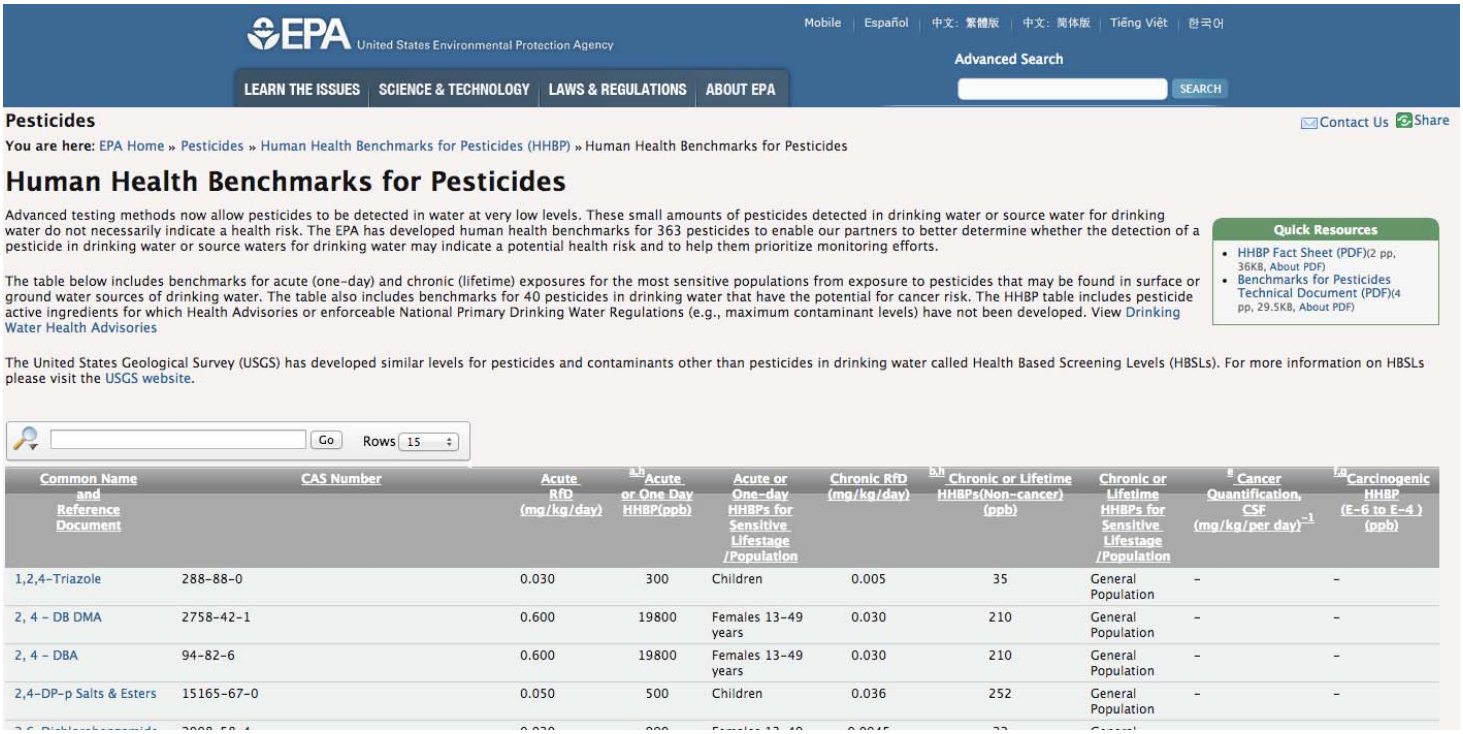
Holman and Gray: Human and Ecological Risk Assessment, 20: 1550–1564, 2014

- 2013年の時点で、農薬352剤について遡及的解析が行われた
  - 殺虫剤 24%　除草剤 37%
    殺菌剤 22%　その他 17%
  - 352は、登録された農薬の正確な数ではないが、傾向を把握するには信頼できる数である（絶対数/パーセンテージではない）



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Pesticides

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Human Health Benchmarks for Pesticides

Advanced testing methods now allow pesticides to be detected in water at very low levels. These small amounts of pesticides detected in drinking water or source water for drinking water do not necessarily indicate a health risk. The EPA has developed human health benchmarks for 363 pesticides to enable our partners to better determine whether the detection of a pesticide in drinking water or source waters for drinking water may indicate a potential health risk and to help them prioritize monitoring efforts.

The table below includes benchmarks for acute (one-day) and chronic (lifetime) exposures for the most sensitive populations from exposure to pesticides that may be found in surface or ground water sources of drinking water. The table also includes benchmarks for 40 pesticides in drinking water that have the potential for cancer risk. The HHBP table includes pesticide active ingredients for which Health Advisories or enforceable National Primary Drinking Water Regulations (e.g., maximum contaminant levels) have not been developed. View Drinking Water Health Advisories

Quick Resources
- HHBP Fact Sheet (PDF)(2 pp, 36KB, About PDF)
- Benchmarks for Pesticides Technical Document (PDF)(4 pp, 29.5KB, About PDF)

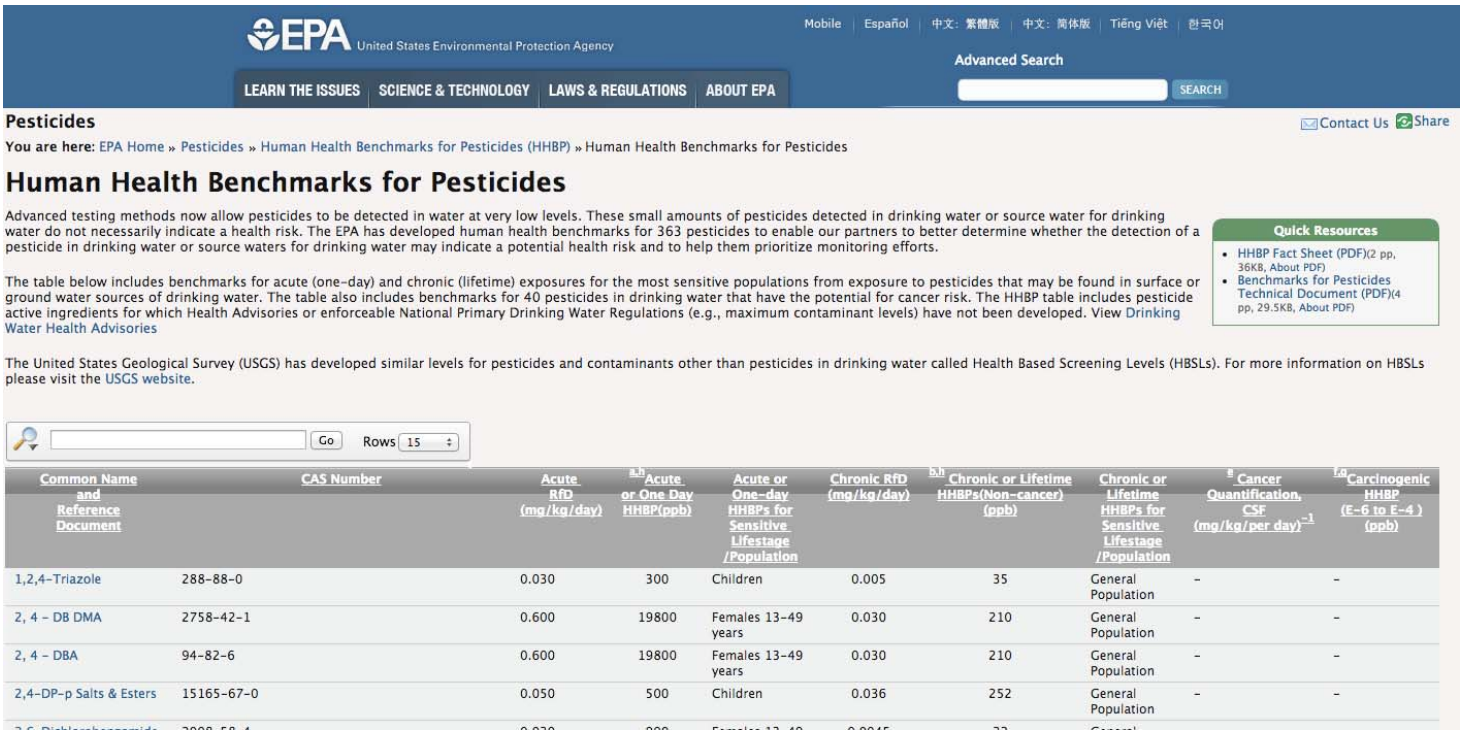
The United States Geological Survey (USGS) has developed similar levels for pesticides and contaminants other than pesticides in drinking water called Health Based Screening Levels (HBSLs). For more information on HBSLs please visit the USGS website.

Go | Rows 15

Common Name and Reference Document	CAS Number	Acute RfD (mg/kg/day)	[a,h] Acute or One Day HHBP(ppb)	Acute or One-day HHBPs for Sensitive Lifestage /Population	Chronic RfD (mg/kg/day)	[b,h] Chronic or Lifetime HHBPs(Non-cancer) (ppb)	Chronic or Lifetime HHBPs for Sensitive Lifestage /Population	[i] Cancer Quantification, CSF (mg/kg/per day)$^{-1}$	[f,g] Carcinogenic HHBP (E-6 to E-4) (ppb)
1,2,4-Triazole	288-88-0	0.030	300	Children	0.005	35	General Population	-	-
2, 4 - DB DMA	2758-42-1	0.600	19800	Females 13-49 years	0.030	210	General Population	-	-
2, 4 - DBA	94-82-6	0.600	19800	Females 13-49 years	0.030	210	General Population	-	-
2,4-DP-p Salts & Esters	15165-67-0	0.050	500	Children	0.036	252	General Population	-	-

ARfDs, chronic RfDs, and cancer risks derived by the USEPA Office of Pesticide Programs (OPP) for 363 pesticides found in sources of drinking water, at http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home

Also visit USEPA OPP website: http://www2.epa.gov/pesticides



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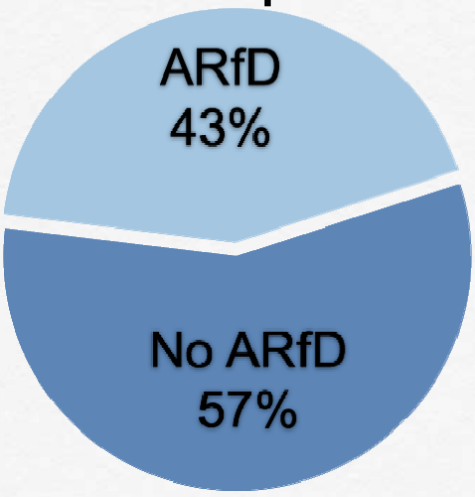
飲料水の原水から検出された363種類の農薬について、農薬プログラム事務局（OPP）が算出したARfD及び慢性RfD（ADI）の数値は、http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:homeに公表されている。

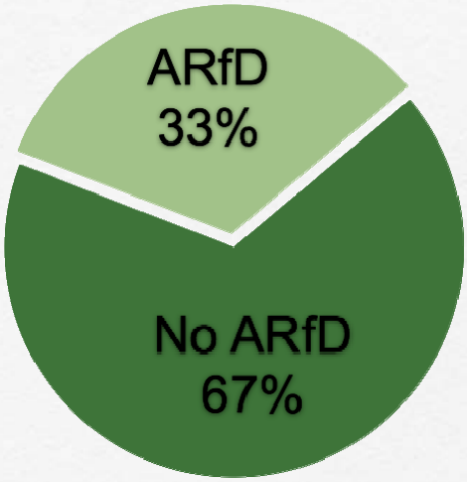
USEPAウェブサイトも参照: http://www2.epa.gov/pesticides

How often is an ARFD necessary?

General Population



Females 13-49 yrs

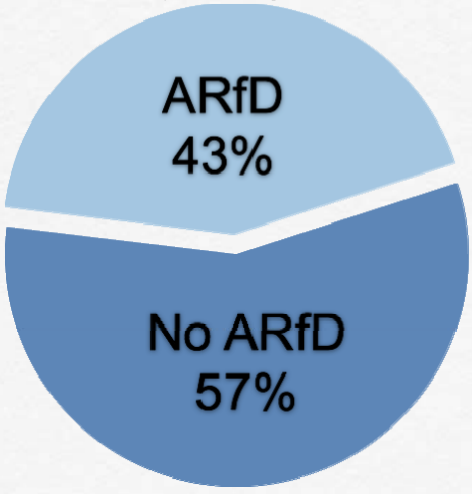


Not all chemicals pose an acute hazard

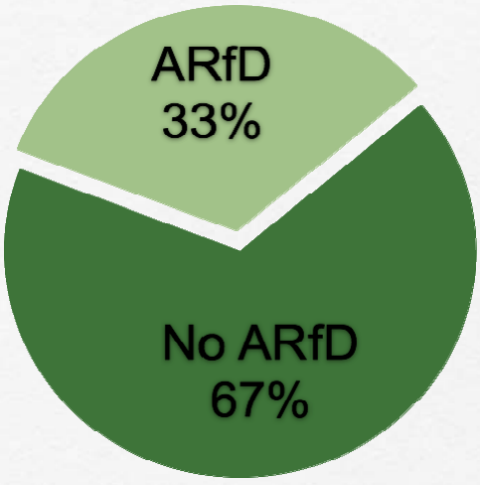
Modified from Holman & Gray, 2014

ARfDが必要となる頻度

一般の集団



13–49歳の女性

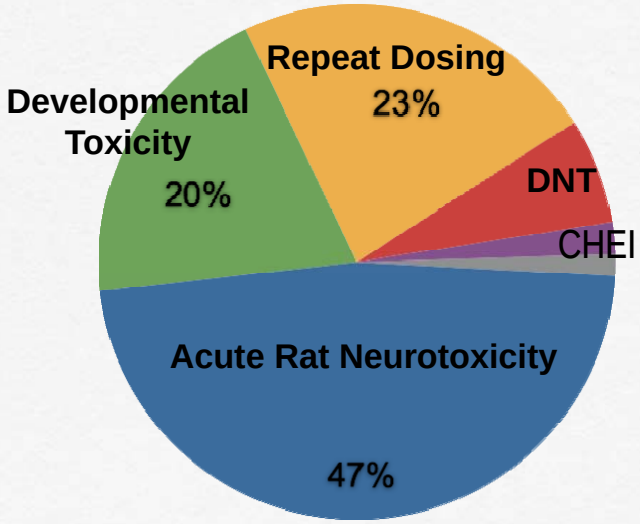


全ての化学物質が急性影響のハザードとなるわけではない

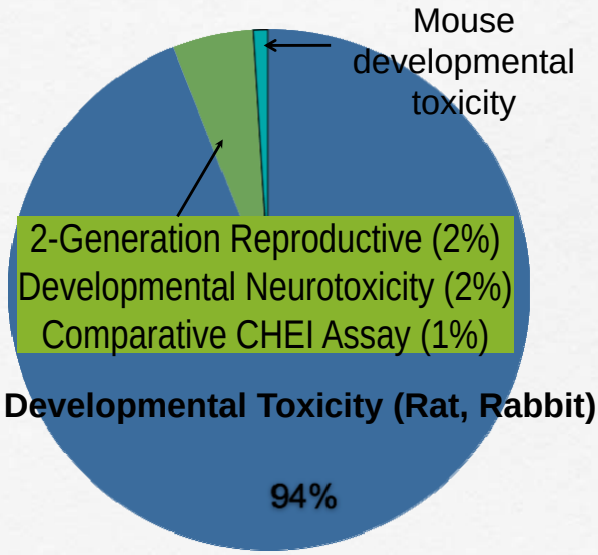
Modified from Holman & Gray, 2014

What studies are used?

General Population



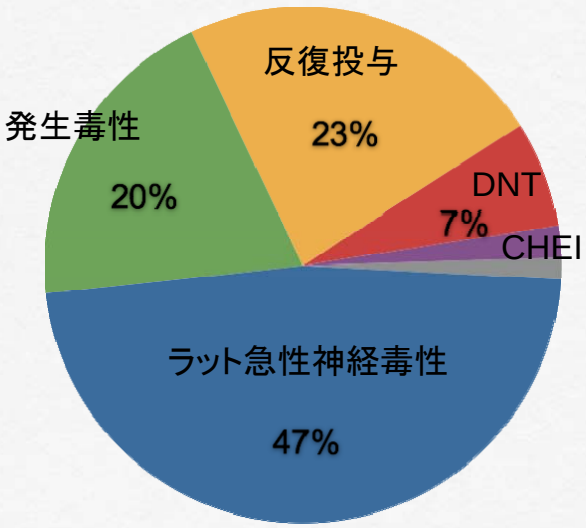
Females 13-49 yrs



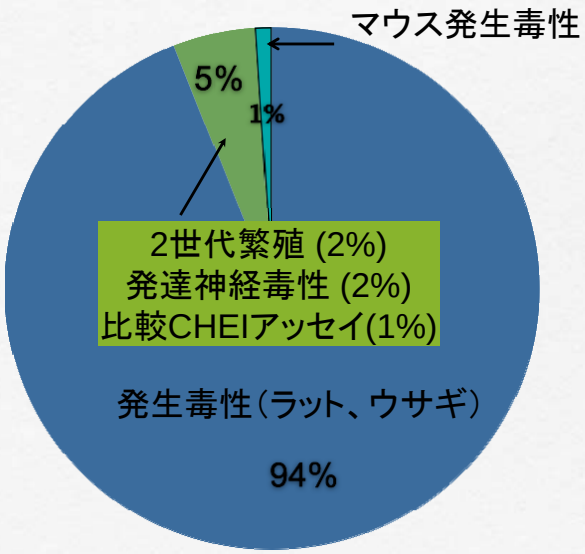
Modified from Holman & Gray, 2014

（ARfD設定に）使用された試験

一般の集団

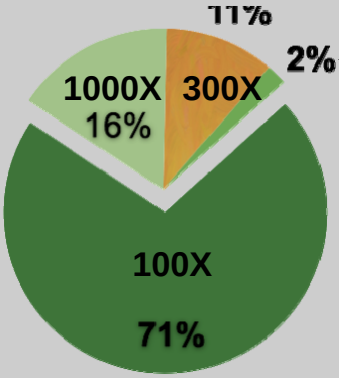


13-49歳の女性



Modified from Holman & Gray, 2014

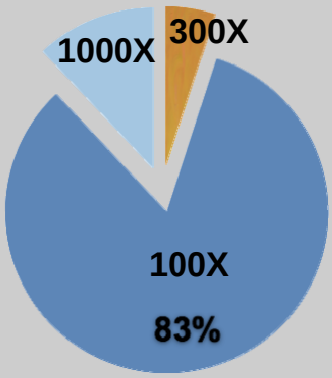
What uncertainty/safety factors are applied?



General Population

(Maximum = 3000X)

USEPA Policy

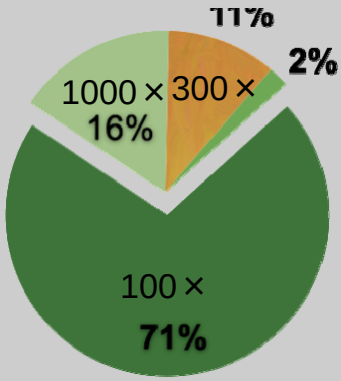


Females 13-49 yrs

- NOAEL identified 86% of the time for general population; 96% for females 13-49 yrs.
- FQPA Safety Factor removed 81% of the time for general population; 84% of time for females 13-49 yrs.

Modified from Holman & Gray, 2014

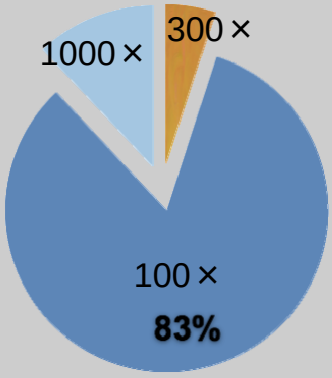
どれくらいの不確実係数／安全係数が適用されたか？



一般の集団

(最大で3000×)

USEPA の方針



13-49歳の女性

- NOAELは、一般の集団で86%、13～49歳の女性の96%に設定
- FQPA安全係数は、一般の集団ので81%、13～49歳の女性の84%で削減

Modified from Holman & Gray, 2014

Selecting Endpoints: Repeat Dose Studies

- Holman and Gray (2014)
  - ARfDs for General Population
    - 18% are derived from subchronic, subchronic neurotoxicity, and chronic toxicity tests.
    - 19.7% from prenatal developmental studies (maternal toxicity).

Appropriate endpoints are selected from repeat dose studies but “typically” following a day or a few days of treatment. (case by case judgements)

エンドポイントの選択：反復投与試験

- Holman and Gray (2014)
  - 一般の集団に対するARfD
    - 18%；亜急性毒性、亜急性神経毒性、慢性毒性試験より算出
    - 19.7%；発生毒性試験の母体毒性より算出

適切なエンドポイントは反復投与試験からも選択されるが、「典型的には」投与1日又は2～3日後に選択。（ケース・バイ・ケースの判断）

Case Examples: Repeat Dose Studies and Relevant Effects

- Examine complete toxicological database Examine early observations.
- Understand time course and dose dependency of responses.
- Consider underlying biology, pharmacokinetics and mode of action of the effect.

事例：反復投与試験と、関連する影響

- 全ての毒性データベースを検討
  初期に観察された影響を検討
- 反応の経時的推移と用量依存性を理解
- 影響の背後にある生物学的現象、薬物動態作用機序を考慮

Case Example: *Mydriasis (Abamectin)

*Abnormal dilation of the pupil.

Pharmacokinetics → **Mode of Action** → **Response**

(Rapid elimination, no accumulation) | (Binding to GABA receptor) | Neurotoxicity

Based on 2011 Risk Assessment found at
http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home

Side Note: 2015 Draft screening analysis for cumulative risk
http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2015-0422-0005

事例: 散瞳* (アバメクチン)

*異常な瞳孔拡張

薬物動態 → **作用機序** → **反応**

(迅速な排泄、蓄積なし) | (GABA受容体への結合) | 神経毒性

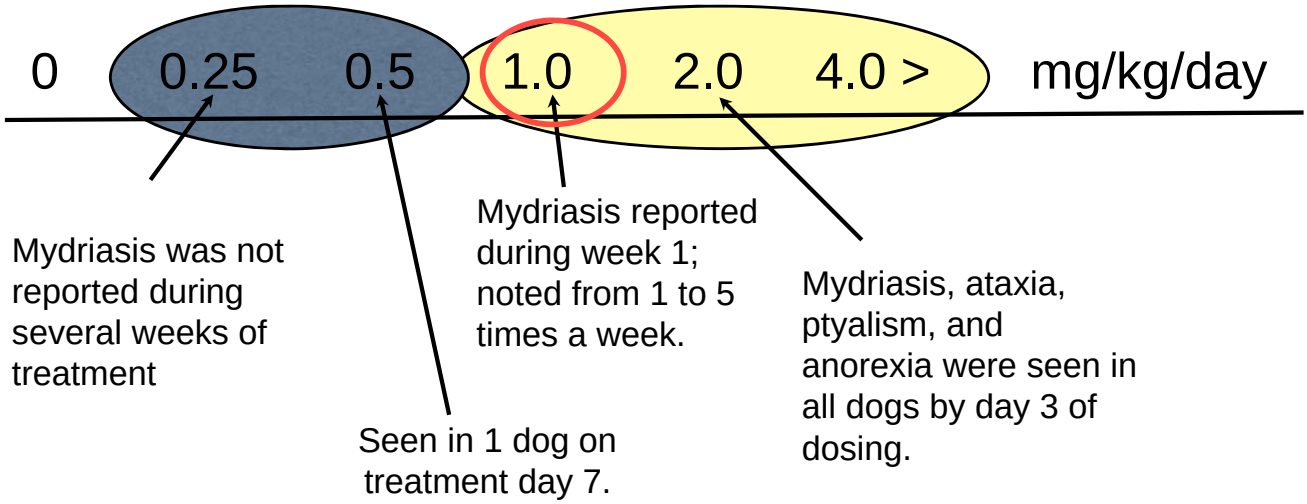
2011年のリスク評価
http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home

注釈: 2015年案・蓄積リスクのスクリーニング解析
http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2015-0422-0005

Abamectin

Observation of Mydriasis in Dog Studies:
12 Week Feeding Study
18 Week Gavage Study
53 Week Feeding Study

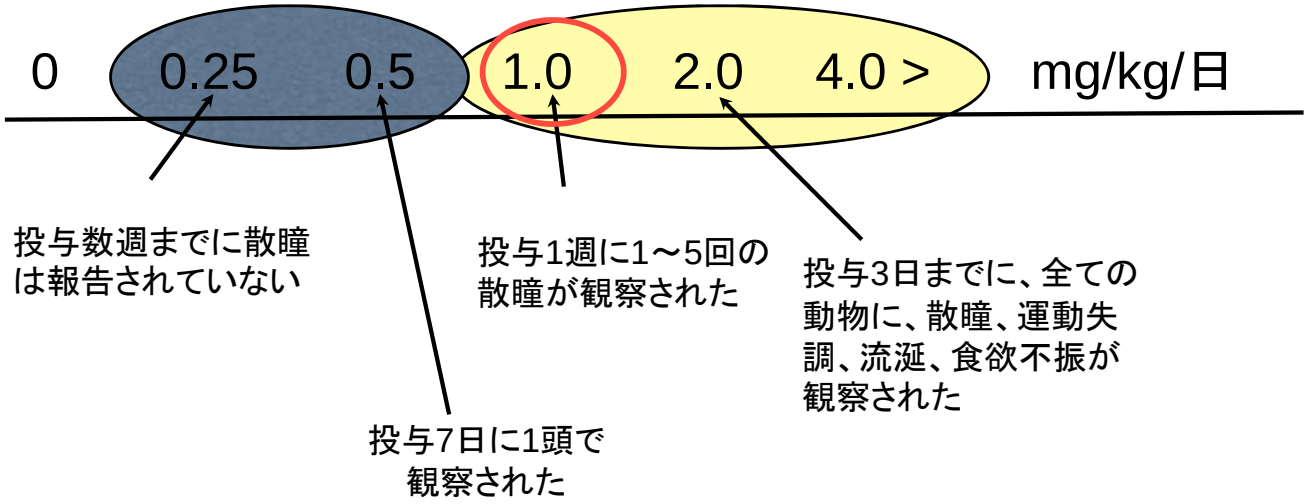
Response is possible after a single dose of 1 mg/kg.



アバメクチン

イヌの試験における散瞳の観察
12週間混餌投与試験
18週間強制経口投与試験
53週間混餌投与試験

1 mg/kgの単回投与後から反応が生ずる可能性



Abamectin

ARfD for General Population, including Infants and Children
ARfD = 0.005 mg/kg/day Based on the possibility of Mydriasis occurring at 1mg/kg bw/day (12 week Dog Study; NOAEL = 0.5 mg/kg) and a 100X Uncertainty Factor. Supported by Reduced Splay Reflex in an Acute Rat Neurotoxicity Study at 1.5 mg/kg/day (NOAEL = 0.5 mg/kg/day)

アバメクチン

乳幼児を含めた一般集団に対するARfD
ARfD = 0.005 mg/kg/日 1 mg/kg 体重/日で散瞳が生じる可能性(イヌへの12週間試験；NOAEL = 0.5 mg/kg)に不確実係数100×を適用 ラットを用いた急性神経毒性試験における1.5 mg/kg/日投与群の開脚反応の減少の結果（NOAEL = 0.5 mg/kg/日）により支持される

Case Example: Methemoglobinemia (Desmedipham)

Based on 2007 Risk Assessment found at
http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home

事例：メトヘモグロビン(MetHb)血症（デスメディファム）

2007年リスク評価より
http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home

Methemoglobin (MtHb) Formation by Desmedipham

- Critical Study: Rat Developmental (maternal effects)
  - Treatment Doses = 0, 10, 100, or 500 mg/kg bw/day and Exposure = Gestation days 6 through15.
    - Dams MtHb was only measured on day 16 of pregnancy
  - Maternal NOAEL = 10 mg/kg bw/day based on increased MtHb at 100 mg/kg/day.
- MtHb formation was common endpoint in toxicological database.
  - Can attribute to a single dose.
- ARfD (General Population) = 0.1 mg/kg bw/day based on a NOAEL of 10 mg/kg bw/day and 100X Uncertainty factor.

デスメディファムによるメトヘモグロビン（MetHb)の形成

- 重要な試験: ラットの発生毒性（母体影響）
  - 投与量 = 0、10、100、又は 500 mg/kg体重/日
    ばく露 = 妊娠6日から15日
    - 母動物のMtHbは、妊娠16日に測定
  - 母動物のNOAEL = 10 mg/kg体重/日
    （100 mg/kg/日投与群のMetHbの増加を根拠）
- MtHbの形成は、毒性データでは一般的なエンドポイント
  - 単回投与によると考えうる
- ARfD（一般の集団）= 0.1 mg/kg体重/日
  （NOAEL 10 mg/kg体重/日に不確実係数100×を適用）

Topic: Specific Effects

- More about the process of setting ARfDs
  - Fetal effects from developmental studies, including endocrine modes of action.
    - Case Examples
  - General considerations for interpreting decreases in body weight.

トピック: 特定の影響

- ARfDの設定過程に関する補足
  - 発生毒性試験における胎児への影響（内分泌への作用機序を含む）
    - 事例
    - 体重減少を解釈するための一般的な考察

Fetal Effects

- **Assumption**: Single exposure during a critical period of development may cause harm (case by case)
- **Prenatal developmental studies** (most frequently used for females of 13-49 yrs.)
  - fetal death, resorptions, post-implantation loss, malformations and variations, etc.
    - Delay in ossifications - Look at all the findings in the study when interpreting these skeletal variations. (Carney and Kimmel, 2007 Birth Defect Research (Part B) 80:473-496)
      - May be of low significance when associated with maternal toxicity following repeat dosing and especially occurring late in gestation.

胎児への影響

- **仮定**: 発達の臨界期における単回ばく露が悪影響を及ぼす（ケースバイケース）
- **発生毒性試験**（13-49歳の女性に最も頻繁に適用)
  - 胎児死亡、胚吸収、着床後吸収胚、奇形、変異、その他
    - 骨化遅延 - 骨格変異を解釈する際、得られた全ての所見を確認 (Carney and Kimmel, 2007 Birth Defect Research (Part B) 80:473-496)
      - 反復投与及び特に妊娠後期に生ずる母毒性に起因する場合は（臨界期暴露との関連は）低い可能性

Developmental Toxicity of Endocrine Active Chemicals

- Data Sources
- Principles for Evaluating
- Case Studies

USEPA Endocrine Disruptor Screening Program (EDSP)
Visit Website: http://www2.epa.gov/endocrine-disruption

内分泌活性化学物質に係る発生毒性

- データソース
- 評価の基準
- 事例

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Visit Website: http://www2.epa.gov/endocrine-disruption

Endocrine Active Chemicals (Data Available)

- **Traditional Test Guideline Data, Literature**
- **EDSP Tier 1** studies - Screens potential chemical interaction with estrogen, androgen, or thyroid hormone pathways (Not intended for risk assessment; provides insight into endocrine mode of action)
  - Guidance for evaluating Tier 1 results to identify need for Tier 2 testing - http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2010-0877-0021
  - EPA recently released its evaluation of Tier 1 screening results for 52 pesticides: http://www2.epa.gov/ingredients-used-pesticide-products/endocrine-disruptor-screening-program-tier-1-assessments#find-results
- **Tier 2 Testing** - Characterize effects and dose-response for risk assessment (e.g., 2-generation reproductive study..

内分泌活性化学物質 (データ入手可能)

- **従来のテストガイドラインに基づくデータ, 文献**
- **EDSP Tier 1** 試験 -エストロゲン、アンドロゲン、甲状腺ホルモン経路と相互作用をもたらす可能性のある化学物質のスクリーニング（リスク評価向けではなく、内分泌作用機序に関する知見を深めるため）
  - Tier 2試験の必要性を確認するためのTier 1 の結果の評価のためのガイダンス http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2010-0877-0021
  - EPAは最近52農薬のTier 1スクリーニング結果の評価を公表した。http://www2.epa.gov/ingredients-used-pesticide-products/endocrine-disruptor-screening-program-tier-1-assessments#find-results
- **Tier 2 試験** – リスク評価のため、影響及び用量-反応関係を特定する（例：2世代繁殖試験）

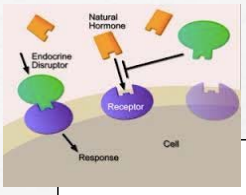
US EDSP Tier 1 Assays	Receptor Binding				Steroidogenesis		HPG Axis	HPT Axis
	E	Anti-E	A	Anti-A	E	A		
In Vitro								
ER Binding	✔	✔						
ER∝ TransAct	✔							
AR Binding			✔	✔				
Steroidogenesis					✔	✔		
Aromatase (inhib)					✔			
In Vivo								
Rat Uterotrophic	✔							
Rat Hershberger			✔	✔		✔		
Rat Male Pubertal			✔	✔		✔	✔	✔
Rat Female Pubertal Ra	✔	✔			✔		✔	✔
Fish Short Term	✔	✔	✔	✔	✔	✔	✔	
Amphibian Metamorphosis								✔

US EDSP Tier 1アッセイ	受容体結合				ステロイド産生		HPG 軸	HPT 軸
	E	抗E	A	抗A	E	A		
In Vitro								
エストロゲン受容体結合	✓	✓						
エストロゲン受容体の転写活性	✓							
アンドロゲ受容体結合			✓	✓				
ステロイドホルモン合成経路					✓	✓		
アロマターゼ（阻害）					✓			
In Vivo								
ラット　子宮肥大	✓							
ラット　ハーシュバーガーアッセイ			✓	✓		✓		
ラット　性成熟　雄			✓	✓		✓	✓	✓
ラット　性成熟　雌	✓	✓			✓		✓	✓
魚類　短期	✓	✓	✓	✓	✓	✓	✓	
両生類変態								✓

ARfD: Endocrine Active Chemicals

Some guidance for setting ARfDs can be found in Solecki et al. Food and Chemical Toxicology 43 (2005) 1569–1593.

- Basic principles of toxicology:
  - biology of the system.
  - mode of action/toxicokinetics.
  - critical windows of susceptibility.
  - ability of the organism to compensate.
  - redundancy in the system.
  - biological half life of hormone relative to length of critical window.

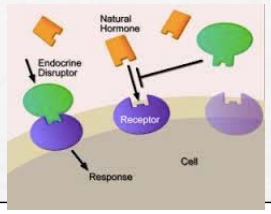


Note:
Molecular or hormonal changes may or may not lead to an adverse event. It is important to understand linkage to functional, morphological and behavioral changes.

ARfD: 内分泌活性化学物質

ARfDs 設定のガイダンス： Solecki et al. Food and Chemical Toxicology 43 (2005) 1569–1593.

- 毒性学の基本原理:
  - 組織生物学
  - 作用機序 / トキシコキネティクス
  - 感受性の臨界期
  - 生物の回復能力
  - システムが有する冗長性
  - 臨界期の長さと関連するホルモンの生物学的半減期



注:
分子学的変化又はホルモンの変化は有害影響につながる可能性があるが必ずしもそうではない。機能的・形態学的・行動学的変化との関連を理解することが重要である。

Thyroid Hormone Pathway (Mancozeb)

- "A single dose of a chemical that perturbs thyroid homeostasis would not be expected to impact tissue function due to the buffering of thyroid hormone concentrations by homeostatic mechanisms."
  - Acute Dietary (Females 13 – 49) - Used rat developmental toxicity study based on hydrocephaly and other malformations.
  - Acute Dietary (general population) - no appropriate endpoint identified.
  - Chronic Dietary (all populations) and Oral (Short- or Intermediate-Term) based on thyroid effects.

↑Hepatic clearance of TH

↓TH levels

↑ TSH levels

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甲状腺ホルモンの経路 (マンコゼブ)

- 「甲状腺の恒常性をかく乱する化学物質の単回投与は、恒常性機能のメカニズムにより恒常性ホルモンの濃度が保護されるため、組織の機能に影響を与えない。」
  - 急性（13 – 49歳の女性） – ラット発生毒性試験における水頭症及び他の奇形を根拠
  - 急性（一般の集団） – 適切なエンドポイントは同定されず
  - 慢性（全ての集団）及び短期もしくは中期の経口投与甲状腺の影響を根拠

↑甲状腺ホルモン（TH）の肝クリアランス

↓甲状腺ホルモン（TH）レベル

↑甲状腺刺激ホルモン（TSH）レベル

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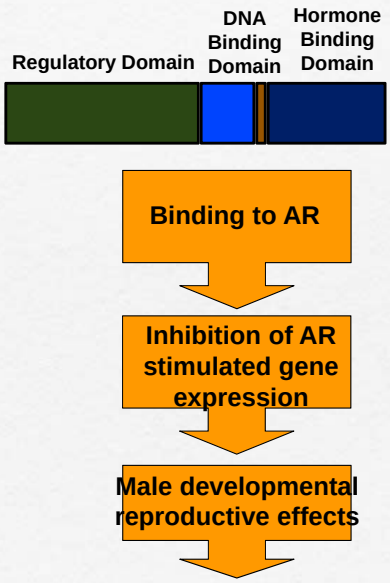
Androgen Hormone Pathway (Vinclozolin)

- Acts as a competitive antagonist at the androgen receptor.
- A single chemical dose during a critical window can potentially lead to abnormal development.
  - Acute Dietary (Females 13 – 49 yrs.); rat developmental rat study based on most sensitive indicator of acute anti-androgenic developmental toxicity.
  - Acute Dietary (General population); effects resulting from a single dose were not observed.



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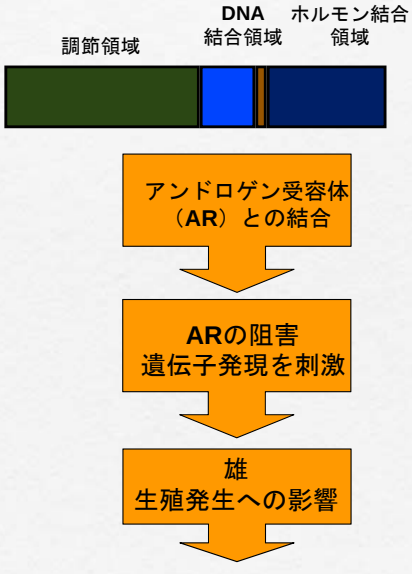
アンドロゲンホルモンの経路（ビンクロゾリン）

- アンドロゲン受容体の競合的拮抗剤として作用
- 臨界期の単回投与は発生異常をもたらす可能性がある。
  - 急性（13 – 49歳の女性）; ラット発生毒性試験において最も感受性の高い指標である抗アンドロゲン作用の急性発生毒性を根拠
  - 急性（一般の集団）; 単回投与による影響は見られなかった



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Effects on Body Weight (usually reductions)

体重への影響（通常は減少）

Some general points about interpreting body weight (BW) changes

- BW decreases - Consider with other information (includes toxicokinetics, mode of action, food consumption).
  - food efficiency = change in body weight divided by the change in food consumption.
- Examine all data.
  - individual animal data, absolute BW gains between groups, mean BW gains relative to controls, different time points.
- Look for dose response relationships.
- Consider both statistical and biological significance.

体重変化の解釈についての一般的なポイント

- 体重減少 – 他の情報と併せて考察する(トキシコキネティクス、作用機序、摂餌量を含む)
  - 食餌効率:体重の変化を摂餌量の変化で除す
- 全てのデータを確認
  - 動物の個体別データ、群間の絶対体重増加量、対照群と比較した平均体重増加量、異なる測定時期
- 用量反応関係を求める
- 統計学的及び生物学的優位差の両方を考慮

ARfD: Body Weight (BW) as a Relevant Endpoint

- Acute Neurotoxicity Study
  - It is a single dose study.
- Repeat Dose Studies
  - A decrease in BW may not be due to a single dose.
  - Look for early observations (following at most a few days of dosing).

ARfD: 体重を関連するエンドポイントとしてとらえる

- 急性神経毒性試験
  - 単回投与の試験である
- 反復投与試験
  - 体重減少は単回投与に起因するとは限らない
  - 投与開始初期の変化を観察を観察 (特に投与開始から数日間)

ARfD: Body Weight (BW) - continued

- **Prenatal Developmental Studies**
  - **Deceases in Fetal BW** - Its indicator of in utero toxicity.
    - Important that all the findings in study (maternal toxicity, other fetal effects) be considered in interpreting this effect.
    - Typically used only along with other developmental effects as basis for setting ARfDs.
      - e.g., " Decreased fetal body weights and increased incidence of litters and fetuses with developmental variations."
  - **Decreases in Maternal BW**
    - Dams are evaluated frequently (3 day intervals) for BW and Food Consumption.
      - If it is an early observation, e.g., "...on GD9 (days 1-3 of dosing) of decrease BW", should be considered for ARfD setting.

ARfD: 体重 – 続き

- **（胎児）発生毒性試験**
  - **胎児体重の減少**- 子宮内毒性の指標
    - 影響を解釈する上で試験の全ての所見（母毒性、他の胎児への影響）を考慮することが重要
    - ARfDの設定根拠として通常、他の発生影響とのみ併用
      - 例）胎児体重の減少と産児数や変異を有する胎児数の増加
  - **母動物の体重減少**
    - 母動物の体重と摂餌量は頻繁に（3日毎）に評価される
      - もし初期（例えば：妊娠9日（投与1-3日））に体重減少が観察されればARfDの設定根拠として考慮すべき。

Case Example: Human Data

Intentional human dosing studies may improve the accuracy of the RfD and provide information about species differences, but must meet ethical and scientific standards.

ARfDs: Rat > Dog > Rabbit > Mouse > Humans (1%)

2006 EPA Rule: Protections for Subjects in Human Research

EPA must rely on independent Human Studies Review Board (HSRB) to obtain expert peer review

http://www2.epa.gov/osa/human-studies-review-board

事例: ヒトのデータ

意図的なヒトへの投与試験は参照用量（RfD）の正確性を向上させ、種差の情報を提供する可能性はあるが、倫理的及び科学的基準を満たす必要がある。

ARfD: ラット > イヌ > ウサギ > マウス > ヒト（1%）

2006年EPA 規則：ヒト試験の対象者の保護

EPA は独立性を有する「ヒト試験の審査委員会（HSRB）」に諮問し、専門家のピアレビューを受ける必要

http://www2.epa.gov/osa/human-studies-review-board

Ethephon

- Intentional dosing studies suggest humans may be more susceptible than laboratory animals
  - 28 day study with daily bolus dosing (capsule) of adults
  - Cholinergic signs seen between days 1-4 at LOAEL of 1.8 mg/kg/day.
- ARfD for general population = 1.8 mg/kg (LOAEL)/30X = 0.06 mg/kg
  - 30X = 10X for interspecies extrapolation not necessary and 3X factor for the lack of a NOAEL.

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エテホン

- 意図的な投与試験はヒトの感受性が実験動物と比べ、より高い可能性を示唆
  - 成人への28日間ボーラス投与（カプセル）試験
  - 1.8mg/kg/日以上投与において、投与1-4日にコリン作動性の兆候が認められた。
- 一般の集団に対するARfD＝1.8mg/kg（LOAEL）/30×＝0.06 mg/kg
  - 30×= 種間の外挿である10×は不要、NOAELが得られていないための3×（を追加）

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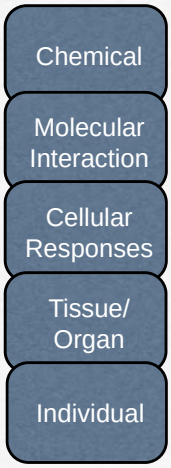
Concluding Remarks

おわりに

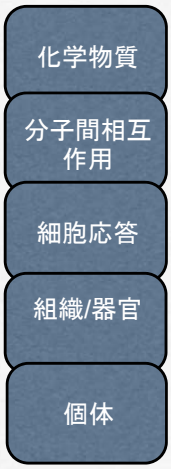
Future Directions: 21st Century Paradigms: Faster, More Reliable and Interpretable



Key events along a biological continuum within a MoA/AOP

- Shift toward mechanistic approaches (rather than extensive animal testing.)
  - Develop knowledge of adverse outcome pathways (AOP) or modes of action (MoA), for example,
    - strengthen formation of chemical categories based on shared biological and structured properties for read-across methods
    - support test method development (e.g., in vitro data and computational modeling)

今後の方向性: 21世紀のパラダイム: 迅速に、信頼性及び説明性を高める



MoA/AOPの生物学的連続性の中での主な事象

- メカニスティック・アプローチへの転換（広範囲の動物実験を用いるよりも）
  - 悪影響へのパスウェイ（AOP）又は作用機序（MoA）についての知見を深める　例えば;
    - Read Across手法の展開のため、生物学的性質、構造特性の類似性に基づく化学物質のカテゴリー形成の強化
    - 試験法の開発の支援　例）*in vitro* データ及びコンピューターモデリング

Last Point
Process of Setting ARfDs

- Sometimes the process is uncomplicated.
- Sometimes the process is challenging with difficult issues.
- The reasoning behind the choices needs to be explained.

最後に
ARfD設定のプロセス

- プロセスはときに複雑ではない
- プロセスはときに困難な課題への挑戦である
- 選択に至った背景の説明が求められる

ご清聴ありがとうございました