資料５－２

米国における経皮・吸入投与による短期毒性試験の要求状況

米国においては、連邦規則コード[1]によりデータ要求を定めている（表を参照）。

反復経皮投与毒性試験については、食用作物へ使用する場合には、原則、21/28 日間の試験が要求され、90 日間の試験については、①皮膚経路が主要な暴露経路になる場合又は②有効成分が経皮経路と経口経路で異なって代謝され、代謝物に毒性がある場合に要求される。他方、非食用作物のみに使用の場合には、90 日間の試験が必須となっている。ただし、ガイダンス[2]では、規制当局が意思決定するのに十分な情報が重要であること、不要な動物実験を回避すること等の理由から、化学物質の毒性又は暴露プロファイルによっては、21/28 日間の試験で十分であるとされている。

反復吸入毒性試験については、「ガス、蒸気あるいはエアゾールのように農薬への重要な反復吸入暴露の可能性がある場合に要求する」としており、原則、90 日間の試験を採用しているが、暴露量や暴露期間を考慮の上で、より短い試験期間であっても、評価には十分な場合があり、申請者は当局と相談すべきとしている。

表：§158.500　Toxicology data requirements table（抄）

Guideline Number	Data Requirements	Use Pattern		Test substance to support		Test Note No.
		Food	Nonfood	MP	EP	
Subchronic Testing						
870.3200	21/28-day Dermal	R	NR	TGAI	TGAI and EP	10, 11
870.3250	90-day Dermal	CR	R	TGAI	TGAI and EP	11, 12
870.3465	90-day Inhalation - rat	CR	CR	TGAI	TGAI	13, 14

R = Required; CR = Conditionally required; NR = Not required; MP = Manufacturing-use product; EP = End-use product; TGAI = Technical grade of the active ingredient

10. Required for agricultural uses or if repeated human dermal exposure may occur. Not required if an acceptable 90-day dermal toxicity study is performed and submitted.
11. EP testing is required if the product, or any component of it, may increase dermal absorption of the active ingredient(s) as determined by testing using the TGAI, or increase toxic or pharmacologic effects.
12. Required for food uses if either of the following criteria is met:
    (i) The use pattern is such that the dermal route would be the primary route of exposure; or
    (ii) The active ingredient is known or expected to be metabolized differently by the dermal route of exposure than by the oral route, and a metabolite is the toxic moiety.
13. Required if there is the likelihood of significant repeated inhalation exposure to the pesticide as a gas, vapor, or aerosol.
14. Based on estimates of the magnitude and duration of human exposure, studies of shorter duration, e.g., 21- or 28-days, may be sufficient to satisfy this requirement. Registrants should consult with the Agency to determine whether studies of shorter duration would meet this requirement

[1] Data requirements for pesticide, the Code of Federal Regulations (CFR) at 40 CFR Part 158（URL：https://www.ecfr.gov/cgi-bin/text-idx?SID=738c16c85042ce20aec41a65fa12977e&node=40:24.0.1.1.9&rgn=div5）

[2] Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies（URL：https://www.epa.gov/sites/production/files/2014-02/documents/part158-tox-data-requirement.pdf）

Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies（抄）

II. Background の第２段落

Consistent with OPP's Guiding Principles for Data Requirements, the goals of this document are to ensure there is sufficient information to reliably support registration decisions that are protective of public health and the environment while avoiding the generation and evaluation of data that does not materially influence the scientific certainty of a regulatory decision. It is important to only require data that adequately inform regulatory decision making and thereby avoid unnecessary use of time and resources, data generation costs, and animal testing. Delayed regulatory decisions affect the delivery of health and environmental protections and access to benefits such as pest management tools and safer products. This guidance promotes the full use of existing knowledge to focus on the data needed for a scientifically sound and credible characterization of a specific pesticide's risk profile for the exposure scenarios of interest and will provide consistency in the determination of toxicology data needs across OPP divisions.

III. Principles for Risk-Based Decisions on Requiring Studies

2) Subchronic (28 or 90-Day) Inhalation Toxicity Study (870.3465)

A repeated dose inhalation toxicity study is conditionally required (CR) if there is likelihood of significant repeated inhalation exposure to the pesticide as a gas, vapor, or aerosol. Based on estimates of the magnitude and duration of human exposure, studies of shorter duration, e.g., 28 days, may be sufficient to satisfy this requirement. Registrants should consult with the Agency to determine whether studies of shorter duration would meet this requirement.

In the absence of a repeated dose inhalation study, the agency frequently relies on oral toxicity studies to conduct inhalation risk assessments. In December 2009, the agency sought expert advice and input from its FIFRA Scientific Advisory Panel (SAP) on issues related to this route-to-route extrapolation approach in the absence of an inhalation toxicity study (i.e., the use of oral toxicity studies for inhalation risk assessment). Based on the SAP's recommendations in the March 2, 2010 Final Report, the agency has increased its focus on the uncertainties associated with route-to-route extrapolation and is presently considering the need for inhalation toxicity studies more frequently.

To determine the need for additional data to address inhalation toxicity, reviewers should use a WOE approach that builds on considerations developed in 20021 and the findings discussed in the 2010 SAP Report2. The WOE approach considers all relevant hazard [toxicity, metabolism and/or pharmacokinetics (PK), human data], physical-chemical properties, and exposure (including the margins of exposure (MOEs) from the most recent risk assessment) information as detailed below:

(i) Physical-chemical properties: Vapor pressure and Henry's law constant are key considerations with respect to exposure from volatilization of the chemical after sprays have settled as these properties relate to volatility.

(ii) Use pattern and exposure scenarios: The degree of inhalation exposure in the form of aerosolized droplets or particles/dusts droplets is influenced by the use pattern and exposure scenarios. The entire array of exposure scenarios should be considered and the scenarios where inhalation exposures are the highest should be identified. Particular consideration should be given to the type of application equipment such as air blast and aerial as well as trigger pump sprays and aerosol can dispensers that are more likely to lead to higher occupational handler inhalation exposure. Particle size of aerosols may be an additional factor to consider for some.

(iii) Margins of Exposure (MOEs): MOEs are calculated using a PoD from an oral toxicity study provide benchmarks for risk concerns. Reviewers generally consider MOEs from 10-100X over the Level of Concern (LOC) in combination with other factors such as use pattern, exposure scenarios, exposure data and assumptions used in the MOE calculations to determine overall risk concerns in the absence of data from an inhalation toxicity study. The Level of Concern (LOC) is generally defined by the total uncertainty/extrapolation factors applied. This often includes the 10X factors for interspecies and intraspecies extrapolation and may include other factors such as the FQPA 10X Safety Factor or a database uncertainty factor. This range of 10X-100X is derived from comments from the SAP in the 2010 report that indicate that toxicity resulting from oral exposure is not always a good predictor of toxicity derived from the inhalation route.

(iv) The Overall Toxicity Profile: The toxicological profile of the subject chemical and the profile of pesticides which share the same MOA and/or are in the same chemical class may provide important information with respect to potential inhalation toxicity. Specifically, if inhalation toxicity data for pesticides which share the same MOA and/or are in the same chemical class suggest more sensitive inhalation effects, an inhalation toxicity study may be required regardless of MOE. Portal-of-entry irritation potential should also be considered for those chemicals showing irritation type effects via the oral or dermal route as these may also result in inhalation toxicity to the respiratory system. Consideration of the acute toxicity data (eye irritation, dermal irritation, sensitization, corrosivity, acute inhalation toxicity) may also inform the concern for localized repeated inhalation effects and metabolism/pharmacokinetic data may inform the concerns for systemic toxicity concerns.

Database Uncertainty Factor (UFDB): If the WOE demonstrates that a subchronic inhalation toxicity study is required, then the 10x UFDB will be retained only for inhalation risk assessment scenarios and relevant durations that may be impacted by the results of this study. Where the 10x UFDB is applied, it would generally be retained until such data become available or other factors support reconsideration of the data requirement (e.g., changes to the exposure potential).

3) Subchronic (21 or 90 Day) Dermal Toxicity (870.3200; 870.3250)

The use pattern determines the requirement for a repeated dose dermal toxicity study [(i.e., Required or Conditionally Required (CR)]. A 21/28-day dermal toxicity study is required for food-use chemicals. The duration of this study is judged to be of adequate duration because higher tiered oral studies (i.e., chronic or carcinogenicity studies) are available which can potentially be used for dermal risk assessments. A 90-day study is required for non-food use chemicals. However, the Agency believes that depending on the toxicological and/or exposure profile of the chemical, the 21/28-day dermal toxicity test may be sufficient in duration. For other chemicals, 21/28-day duration may not be sufficient. For example, professional applicators may be subjected to repeated exposures during the 3 months of peak summer infestations. Since for many pesticides there may be increased toxicity with increased exposure professional applicators may not be adequately protected with a 21/28 day study.

To determine the need for additional data to address dermal toxicity, reviewers should use a WOE approach that considers all relevant hazards (toxicity, metabolism and/or PK, human data), physical-chemical properties, and exposure (including the MOEs from the most recent risk assessment) information as detailed below:

(i) Physical-chemical properties: Molecular weight and log Kow (between -1 and +3.5) are considered in the WOE as these properties can aid in predicting those chemicals with high and low potential for dermal absorption. Other properties to consider include: physical state, solubility in water and non-polar solvents, vapor pressure (< 5 mmHg), and boiling point (liquid/solid) >15 C^{o}.

(ii) Use pattern and exposure scenarios: Scenarios that result in dermal exposure need to be considered in the WOE analysis for granting a waiver for the dermal toxicity study. This should include the product types (e.g., granular, wettable powder, etc) methods of application, exposure duration (short/ intermediate/long-term), and any potential for post-application exposures.

(iii) Dermal absorption study: If an acceptable dermal absorption study is available, a dermal absorption factor (DAF) is derived from that study data. The DAF is used with the oral POD to calculate a dermal equivalent dose (DED). The DED can then be used as the POD in risk assessment in lieu of requesting a repeated dose dermal study.

(iv) Margins of Exposure (MOEs:) MOEs are calculated using a PoD from an oral toxicity study provide benchmarks for risk concerns. Dermal absorption information can be used if available and sufficient quality. Reviewers generally consider MOEs approximately 10X over the LOC1 in combination with other factors such as use pattern, exposure scenarios, exposure data and assumptions used in the MOE calculations to determine overall risk concerns in the absence of data from repeated dose dermal toxicity study. Use of oral studies in deriving MOEs for dermal exposure are often overly conservative, as such, the agency can consider a small margin above the LOC (i.e., 10X) compared to the inhalation study discussed above.

(v) The Overall Toxicity Profile: The toxicity profile of the subject chemical and the profile of pesticides which share the same MOA and/or are in the same chemical class may provide important information with respect to potential dermal toxicity. Consideration of the acute toxicity data (eye irritation, dermal irritation, sensitization, corrosivity, acute dermal toxicity) may also inform the concern for repeated dermal effects and metabolism/pharmacokinetic data may inform the concerns for systemic toxicity concerns.

Database Uncertainty Factor (UFDB): If the WOE does not support granting a waiver of the subchronic dermal toxicity study, then the 10x UFDB will be retained only for dermal risk assessment scenarios and relevant durations that may be impacted by the results of this study. Where the 10x UFDB is applied, it would generally be retained until such data become available or other factors support a reconsideration in the data requirement (e.g., changes to the exposure potential).