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Guidelines for performing systematic reviews in the development of toxicity factors

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ABSTRACT

The Texas Commission on Environmental Quality (TCEQ) developed guidance on conducting systematic reviews during the development of chemical-specific toxicity factors. Using elements from publicly available frameworks, the TCEQ systematic review process was developed in order to supplement the existing TCEQ Guidelines for developing toxicity factors (TCEQ Regulatory Guidance 442). The TCEQ systematic review process includes six steps: 1) Problem Formulation; 2) Systematic Literature Review and Study Selection; 3) Data Extraction; 4) Study Quality and Risk of Bias Assessment; 5) Evidence Integration and Endpoint Determination; and 6) Confidence Rating. This document provides guidance on conducting a systematic literature review and integrating evidence from different data streams when developing chemical-specific reference values (ReVs) and unit risk factors (URFs). However, this process can also be modified or expanded to address other questions that would benefit from systematic review practices. The systematic review and evidence integration framework can improve regulatory decision-making processes, increase transparency, minimize bias, improve consistency between different risk assessments, and further improve confidence in toxicity factor development.

1. Introduction

A systematic review is defined as a high-level review of the available, relevant information in order to extract and analyze all data to address a specific research question. Systematic reviews are becoming an integral part of risk assessments since key steps of the process include using explicit, reproducible methods to identify, select and critically evaluate all quality research in order to minimize bias and provide reliable findings (Cochrane Collaboration, 2011). The use of explicit study inclusion/exclusion criteria is critical in increasing transparency of why particular studies are chosen as potential key studies while others are omitted. Since data are collected from diverse evidence streams (e.g., human clinical data, epidemiological data, animal toxicological studies, mechanistic data), there is a need to evaluate and integrate information from multiple data streams to improve the decision-making process, increase transparency, minimize bias, and improve consistency between different risk assessments.

Several recent publications have proposed best practices for conducting systematic reviews for chemical toxicity assessments (Rhomberg et al., 2013; NRC, 2014; Rooney et al., 2014). For example, the Office of Health Assessment and Translation (OHAT) Division of the National Toxicology Program (NTP), in the National Institute of Environmental Health Services (NIEHS), recently published their method for conducting systematic reviews and evidence integration for reaching hazard identification conclusions (Rooney et al., 2014). The overall objective of this guidance is to provide information on conducting a systematic review in concurrence with the development of chemical-specific toxicity factors based on evidence from human, animal, and mechanistic studies. Fig. 1 depicts the TCEQ systematic review and evidence integration process. In general, derivation of chemical reference values (ReVs) or unit risk factors (URFs) begins with a toxicity assessment involving hazard identification, dose-response assessment, and the evaluation of a chemical's mode of action. The toxicity factors developed by the TCEQ are derived to protect potentially sensitive populations, such as children, pregnant women and the elderly; thus, all available health endpoints and various types of studies are considered in order to determine the most sensitive health endpoint (i.e., critical effect) in the most [relevant or] sensitive species. This guidance, in principle, must also be applicable for chemicals for which limited toxicity data are

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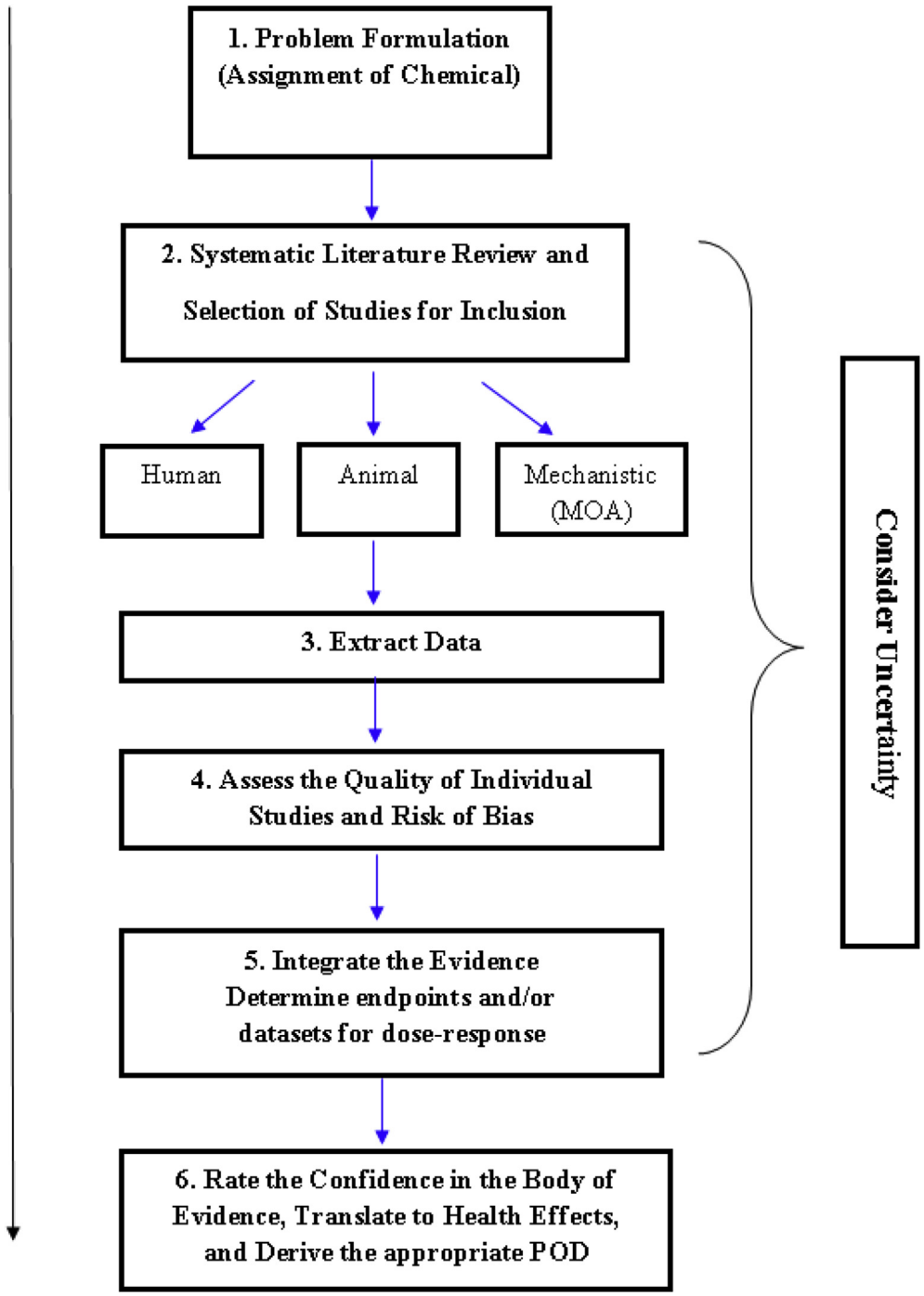

Fig. 1. Steps in systematic review and evidence integration.

available. Therefore, the TCEQ used the available existing methodologies to develop guidelines for conducting systematic reviews and integrating evidence when developing chemical-specific reference values (ReVs) and unit risk factors (URFs).

2. Systematic review and evidence integration framework

2.1. Problem formulation

The first step in the systematic review and evidence integration process is problem formulation (Fig. 1). This step identifies and specifically states the research question and describes the extent of the evaluation. Problem formulation contains elements that promote transparency and consistency, and can accommodate different biologically plausible hypotheses (Rhomberg et al., 2013).

For the derivation of toxicity factors, the TCEQ reviews all available data to identify the critical effect that occurs at the lowest human equivalent concentration or dose. The TCEQ's Guidelines to Develop Toxicity Factors (TCEQ, 2015) is a peer-reviewed publication that outlines the process of critically evaluating a variety of health outcomes and focusing resources on human-relevant adverse health endpoints. The process begins with the selection of a chemical, followed by the review of the physical and chemical properties and a critical review of dose-response data for all of the