Reproductive Toxicology 33 (2012) 410–418

Contents lists available at SciVerse ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Mode of Action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and Human Relevance

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ARTICLE INFO

Article history:
Received 1 April 2011
Received in revised form 1 October 2011
Accepted 24 October 2011
Available online 22 November 2011

Keywords:
Perfluorooctanoic acid
Liver
Leydig cell
Pancreas
Mode of Action
PPARα
Cancer

ABSTRACT

Perfluorooctanoic acid (PFOA) is an environmentally persistent chemical used in the manufacturing of a wide array of industrial and commercial products. PFOA has been shown to induce tumors of the liver, testis and pancreas (tumor triad) in rats following chronic dietary administration. PFOA belongs to a group of compounds that are known to activate the PPARα receptor. The PPARα activation Mode of Action was initially addressed in 2003 [9] and further refined in subsequent reviews [92–94]. In the intervening time, additional information on PFOA effects as well as a further refinement of the Mode of Action framework warrants a re-examination of this compound for its cancer induction Mode of Action. This review will address the rodent (rat) cancer data and cancer Mode of Action of PFOA for tumors of the liver, testes and pancreas.

1. Introduction

The Mode of Action/Human Relevance framework is a tool for selecting and organizing the salient information needed in scientifically based hazard identification and characterization. The Mode of Action/Human Relevance framework for cancer causing materials was initially developed through the efforts of the International Life Sciences Institute Risk Sciences Institute (ILSI RSI) and the International Programme on Chemical Safety (IPCS). This framework provides a systematic analytical tool to identify, organize and evaluate experimental information in rodents pertinent to the hazard characterization in humans. Further development and refinement of the IPCS ILSI RSI framework has been performed including the application to non-carcinogenic materials [1–5]. This framework has been widely accepted internationally and in the US for cancer risk guidance and assessment. This approach has been applied to both cancer and non-cancer toxicological endpoints [1–5].

Mode of Action analysis involves a series of key biological events (key events) that sequentially and temporally produce an observed toxicological effect. Key events are supported by experimental information and available mechanistic data. The use of the Mode of Action framework in the evaluation of toxicity including carcinogenesis is designed to help organize the pertinent and available experimental information and reveal the key events involved in the progression from a normal cell to a neoplastic cell. Differentiating between the terms Mode of Action and mechanism of action is important with respect to the amount of data needed to define the key events. Mode of Action is the biologically plausible series of key events that lead to an adverse effect. Key events are those that are critical to the adverse outcome (i.e., necessary but not necessarily sufficient in their own right), measurable and repeatable. Mechanism of action, in contrast, relates to understanding of the molecular basis of adverse effects. There is limited understanding of the exact mechanisms of toxicity for most adverse effects.

A diagram for the Mode of Action framework approach is provided in Fig. 1. In this model, the weight of evidence of a hypothesized MOA of a toxic endpoint (cancer in this case) observed in animals is considered in reference to those key events that are needed for this toxicological pathway to proceed. Dose–response, temporal concordance, consistency, specificity and biological plausibility of the key events are important features of the Mode of Action analysis. A foundation of the framework is the evaluation of the weight of evidence for defining a Mode of Action in animals and the determination of the applicability of the animal Mode of Action to Human Relevance. If the weight of evidence for the hypothesized Mode of Action is deemed sufficient and relevant to humans, dose–response analysis is then considered in the context of kinetic and dynamic data.

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doi:10.1016/j.reprotox.2011.10.014

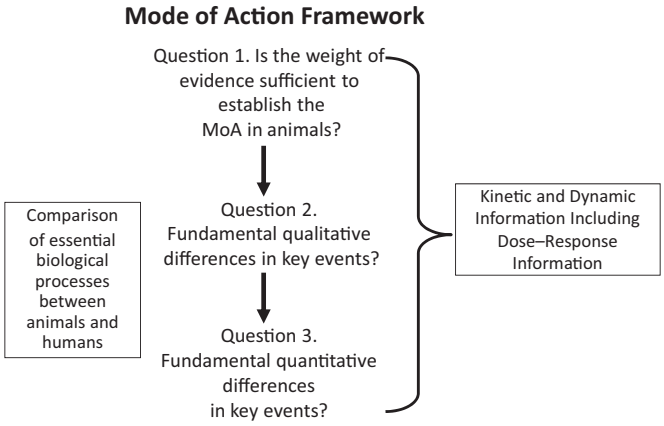

Fig. 1. The Mode of Action (MOA) framework. MOA is considered using the key events of the toxicity pathway. Dose–response and temporal concordance between the key events and the toxic endpoint including consistency, specificity and biological plausibility of the events are included in the framework.

In addition, the framework helps to identify those missing data that will support or refute the proposed Mode of Action. Application of the Mode of Action framework has proven to be an important approach in hazard characterization and allows for the subsequent incorporation of dose–response analysis for relevant human populations, including sensitive subpopulations. This allows for the enhanced coordination of epidemiological and toxicological research as well as allowing for the identification of critical data gaps that likely inform quantitation of risk for human populations of interest.

1.1. Carcinogenesis modes of action

For the induction of cancer by chemicals several possible modes of action have been identified that are applicable to the development of neoplasms (Table 1). These include: (1) DNA reactivity pathways – either through direct (no metabolism of the compound) or indirect (metabolism of the compound into a proximate and/or ultimate form) interaction which eventually results in a mutational event and (2) non-DNA reactivity pathways, which includes cytotoxicity, receptor-mediated, oxidative damage, inflammation or infection pathways.

1.2. Background

PFOA is a perfluoroalkylchemical used in the manufacturing of a wide array of industrial and commercial products. PFOA has been principally used as a surfactant and emulsifier in the production of fluoropolymers specifically polytetrafluoroethylene. Perfluoroalkyl polymers have also been used in the manufacture of non-stick coatings on cookware. PFOA does not readily breakdown in the environment due to the presence of strong carbon–fluorine bonds, and can lead to bioaccumulation in fish, animals and humans. Perfluoroalkyls, especially PFOS and PFOA, have been released into the environment around fluorochemical facilities, leading to human exposure through drinking water [21]. Due to its environmental persistence, coupled with occupational exposure, the potential for human exposure exists. The carcinogenic potential of PFOA in rodents has been investigated in dietary carcinogenicity studies in rats [6]. Based on the results of these studies there is evidence that PFOA is tumorigenic in rodents. Carcinogenicity studies in Sprague-Dawley rats show that PFOA induces a "tumor triad" similar to several PPARα agonists [6,92–94]. This "tumor triad" includes adenomas of the liver, testis (Leydig cell tumors), and pancreas (acinar cell tumors).

While an apparent increase in mammary fibroadenomas was suggested from the chronic rodents studies in Sprague-Dawley rats, upon further pathology review the incidences seen were comparable to the historical background incidence for this strain. In humans, epidemiology studies of workers have not revealed a statistically significant increase in cancer; however, a positive trend for prostate and pancreatic cancer was suggested when comparing non-exposed to probably/definitely exposed workers [7]. Similarly, a cross-sectional study of the Danish population suggested an association for prostate and pancreatic cancer when comparing the highest to the lowest quartile of PFOA exposure [8]. While a previous report evaluated the carcinogenic Mode of Action framework, new information on PFOA toxicological effects, and refinements to the Mode of Action framework approach warrant the updating of the analysis [9]. The discussion below will focus on the presentation of three hypothesized modes of action for the three tumor types produced in the rat following chronic exposure to PFOA. The three tumor types will be examined separately within the context of a Mode of Action (MOA) framework and the relevance of each Mode of Action to humans.

Table 1
Possible Modes of Action for carcinogenic chemicals.

DNA reactivity
Direct
Indirect
Non-DNA reactivity
Cytotoxicity
Receptor-mediated
PPAR
CAR
Ah
Estrogen
Other hormones
Oxidative stress/damage
Inflammation
Infection

Table 2A
PPAR alpha Mode of Action for PFOA-induced liver tumors in rats.

Key events	Support	Key references
1 Activation of the PPARα receptor	Yes	[34,35]
2. Induction of Cell Growth gene expression in liver	Yes	[36,37]
3. Cell proliferation	Yes	[6,36,42]
4. Selective clonal expansion of preneoplastic hepatic foci	Yes	[43]
5. Liver neoplasms	Yes	[6]

2. PFOA tumor mode(s) of action (MOA)

2.1. Hepatic tumor induction by PFOA

As noted above, PFOA has been shown to induce hepatic tumors in the liver of rats following chronic oral exposure [6]. In this study, the incidence of hepatocellular adenoma in the PFOA treatment group was 13% (10/76), compared to 3% (2/80) and 1% (1/79) in the *ad libitum* and pair-fed controls, respectively. An analysis of the possible modes of action (Table 1) by which PFOA may induce hepatic cancer in the rat shows that PFOA is non-DNA-reactive and functions to induce liver tumors through a non-DNA reactive Mode of Action. The proposed MOA for PFOA-induced liver tumors, based on results from a number of studies, involves the activation of the peroxisome proliferator-activated receptor α (PPARα) [9,33]. The hypothesized liver tumor MOA for PFOA involves five key events (Table 2A). These key events are activation of PPARα, which results in the up regulation of specific subsets of genes; those involved