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Assessment of petroleum streams for thyroid toxicity

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HIGHLIGHTS

- 19 petroleum streams were assessed for thyroid effects, from 349 animal studies.
- 3 studies found effects related to thyroid toxicity, related to high aromatic content.
- Two human studies reported significant but weak associations with thyroid cancer.
- The 19 petroleum streams presented a low potential for thyroid effects or toxicity.

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ABSTRACT

The thyroid gland, and its associated endocrine hormones, is a growing area of interest in regulatory toxicology due to its important role in metabolism, growth and development. This report presents a review of the toxicology data on chemically complex petroleum streams for thyroid hormone effects.

Toxicological summaries and studies from all available published and un-published sources were considered, drawing upon the European REACH regulatory submissions for 19 petroleum streams, with in depth review of 11 individual study reports and 31 published papers on related products or environmental settings. Findings relevant to thyroid pathology or thyroid hormone homeostasis were specifically sought, summarized, and discussed. A total of 349 studies of 28-days or longer duration were considered in the review, including data on mice, rats, rabbits, dogs, humans, and fish. The thyroid was almost invariably not a target organ in these studies. Three rodent studies did find thyroid effects; one on a jet fuel product (JP-8), and two studies on a heavy fuel oil product (F-179). The JP-8 product differs from other fuels due to the presence of additives, and the finding of reduced T4 levels in mice in the study occurred at a dose that is above that expected to occur in environmental settings (e.g. 2000 mg/kg). The finding for F-179 involved thyroid inflammation at 10–55 mg/kg that co-occurred with liver pathology in rats, indicating a possible secondary effect with questionable relevance to humans. In the few cases where findings did occur, the polycyclic aromatic hydrocarbon (PAH) content was higher than in related substances, and, in support of one possible adverse outcome pathway, one *in-vitro* study reported reduced thyroid peroxidase (TPO) activity with exposure to some PAH compounds (pyrene, benzo(k) fluoranthene, and benzo(e)pyrene). However, it could not be determined from the data available for this review, whether these specific PAH compounds were substantially higher in the JP-8 or F-179 products than in studies in which thyroid effects were not observed. Thus, a few products may carry a weak potential to affect the thyroid at high doses in rodents, possibly through secondary effects on the rodent liver or possibly through a pathway involving the inhibition of TPO by specific members of the PAH family.

Human epidemiology evidence found weak and inconsistent effects on the thyroid but without identification of specific chemicals involved. Two studies in petroleum workers, which found a lower rate of morbidity and mortality overall, reported a statistically significant increase in thyroid cancer, but the

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small number of cases could not exclude confounding variables as possible explanations for the statistical findings.

Overall, the available data indicates a low potential for thyroid hormone effects from exposure to petroleum streams, especially when the aromatic content is low. Because regulatory studies for most chemicals do not include detailed thyroid function or receptor studies, it remains possible that subclinical effects on this system may exist that were not detectable using conventional pathology or hormone measurements.

1. Introduction

Increasing attention is being paid to assessing the potential for endocrine-mediated effects of possible toxicological relevance to human health and the environment to occur for chemicals in commerce globally. The thyroid gland and its associated endocrine action and physiological regulation are among those systems of increasing interest due largely to its influential role in normal early development and metabolism.

With the increasing interest of regulators and the general public over the potential for androgen, estrogen and thyroid effects of exposures to natural and manufactured substances, this review was undertaken to gather the available information on thyroid findings in studies of petroleum streams and to assess these for product stewardship. There are reports that various chemicals (natural and synthetic) can disrupt thyroid hormonal balance directly and/or indirectly through various mechanisms, and the U.S.EPA has concluded that individuals, particularly in younger stages of development, are potentially vulnerable to adverse effects as a consequence of exposure to thyroid-disrupting chemicals (Miller et al., 2009). Although several types of environmental chemicals have been found to interact with thyroid receptors with potential effects on the developing brain (Zoeller, 2007), petroleum stream chemicals have not been specifically reviewed for thyroid effects.

Petroleum streams represent an array of substances, many with common physical/chemical and toxicological properties that arise from the complexity of the natural source material oils and the variety of products that are formed during the refining and downstream processes (McMillen et al., 2001). Humans may be inadvertently exposed to various petroleum stream products, including such every day products as gasolines and motor oils. Although, in general, most petroleum substances are of low toxicity, local and systemic toxicity has been shown to occur with some of these complex materials. For example, studies have shown that some high boiling point substances (HBPS) can produce systemic and developmental effects in rodents at high doses, and some materials are mutagenic *in vitro* (Gray et al., 2013). Gray and colleagues concluded that some of these effects are related to the profiles of aromatic constituents in these substances (Gray et al., 2013). A similar conclusion formed the basis for predictive modeling of developmental toxicity of HBPS by Murray and associates (Murray et al., 2013a). The developmental effects reviewed by Murray and associates are not known to be related to any thyroid hormonal changes, although this possibility was not the focus of the review.

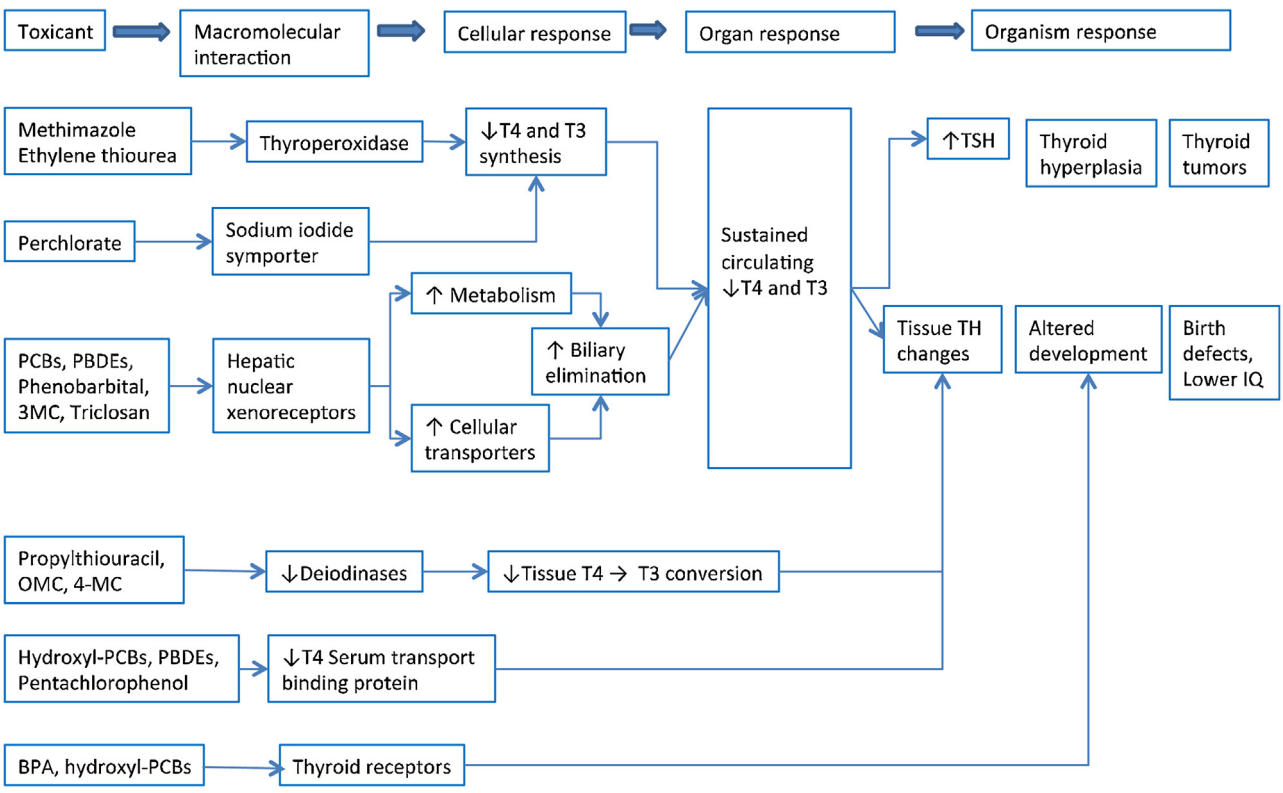

Fig. 1. Adverse outcome pathways for toxic effects on the thyroid gland and hormonal system.