Tox Strategies

Evaluation of Potential Obesogenicity Through a Mode of Action Approach: A Case Study with MTBE

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Abstract:

Background and Purpose: The global rise in the incidences of obesity, a multifactorial disease involving (epi)genetic and environmental factors, and related metabolic diseases are not accounted for by increased caloric intake and lack of exercise alone. Obesity is considered a risk factor for many different diseases including type 2 diabetes, cardiovascular disease, and cancers, among others. There are a number of hypotheses in which specific chemical exposures, especially during critical windows of development, may alter energy metabolism, leading to increased adipose tissue mass, increased body weight gain, and increased susceptibility to obesity. These chemicals are referred to as "obesogens." At this time, there is no regulatory guidance regarding identification of obesogenic chemicals. Thus, an approach for evaluating whether a chemical has properties that might suggest obesogenic activity is needed. The objectives of this review are (1) to identify modes of action (MoAs) for obesity currently reported in the scientific literature to serve as the basis for a framework to evaluate a chemical's potential obesogenic activity, and (2) to evaluate the potential for methyl tert-butyl ether (MTBE), used as a fuel component, to have properties suggesting obesogenic activity.

Methods: First, targeted searches in the peer-reviewed literature were conducted in PubMed using search syntax developed to capture review articles containing MoAs for obesogens. Hand searching of identified reviews was also conducted. From these reviews, potential MoAs for obesity and associated conditions in relation to chemical exposure were identified. Second, targeted searches in PubMed were conducted with syntax specific to MTBE and key terms related to the adverse outcome of obesity and the key events in the identified MoAs to identify relevant mechanistic data from epidemiological studies, *in vivo* animal studies, and *in vitro* assays of MTBE. When publicly available, industry repeated dose toxicity study reports (Guideline, GLP studies) that were not published or for which only a subset of data were published were included in the evaluation. Studies in which MTBE was evaluated as part of a mixture or was administered with overfeeding or in a high fat diet were excluded from this evaluation. Study design details (i.e., doses, duration) and endpoint data identified as key events (e.g., increased adipogenesis, increased blood glucose) that lead to the adverse outcome of obesity (e.g., as indicated by increased body weight) were extracted and mapped to identified obesity MoAs, where possible. The MTBE-specific evidence was reviewed in the context of each identified MoA for obesity, and the total body of evidence was integrated based on the weight of the evidence (WoE) to inform a conclusion regarding the potential obesogenicity associated with exposure to MTBE.

Results: A total of 190 reviews relevant to MoAs for obesogens were obtained from the search in PubMed. The most recent (i.e., those published in the last two years) were prioritized for review and for hand searching to identify other key reviews. A network of MoAs for the adverse outcome of obesity were identified, which included interfering in key events such as adipogenesis, epigenetic alterations, neuroendocrine signaling related to appetite and satiation, adipose tissue function (oxidative stress and

inflammation), adipocyte thermogenesis, lipid metabolism, insulin signaling/insulin resistance, and glucose metabolism/glucose tolerance, as well as interference with the gastrointestinal microbiome. A total of 26 peer-reviewed studies and publicly available study reports were identified that examined endpoints related to potential obesogenic activity of MTBE, including endpoints relevant to the identified MoAs and apical/clinical measures of obesity in human studies (e.g., body weight, waist circumference).

Few studies were identified that directly evaluated key events in the MoAs related to obesity, and there was overall inconsistency in findings for similar endpoints across studies within the evidence base. Only one *in vitro* study was identified in which the differentiation of pre-adipocyte into adipocytes via peroxisome proliferator receptor gamma activation was evaluated. Overall, the epidemiological, animal *in vivo*, and *in vitro* studies did not provide clear evidence regarding the ability of MTBE to alter or interfere in glucose tolerance and insulin sensitivity. Similarly, inconsistent changes in endpoints indicative of altered lipid metabolism were observed across eight studies where rodents were exposed to MTBE. Regarding apical/clinical indicators of obesity (i.e., the adverse outcome), the epidemiological evidence did not show consistent findings in regard to associations between MTBE and increased body mass index (BMI) and waist circumference. Moreover, the available epidemiological studies lack a true comparator (i.e., unexposed) population and cannot establish a temporal relationship between exposure and outcome (i.e., measures of obesity). Finally, there were no *in vivo* animal studies of MTBE exposure in which increased body weight or body weight gain was observed.

Conclusions: An approach for evaluating potential obesogenic activity of a chemical was developed through identification of MoAs for obesity in the published literature, which were used to evaluate if MTBE modulated measures of specific key events within these MoAs. Overall, there were few data relevant to a MoA-based evaluation of the potential obesogenicity of MTBE, and many of the mechanistic and epidemiological data identified were obtained from studies with design and methodological limitations. At this time, limited signals that MTBE elicits any effects on lipid, insulin, and glucose-related processes are inconsistent and weak at best. Thus MTBE-specific data for key events in the identified MoAs and indicators of the adverse outcome (i.e., obesity) do not suggest that MTBE acts as an obesogen.