Toxicology Letters 257 (2016) 38–43

Contents lists available at ScienceDirect

Toxicology Letters

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

Derivation of the critical effect size/benchmark response for the dose-response analysis of the uptake of radioactive iodine in the human thyroid

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HIGHLIGHTS

- Intra-individual variation in the 24-h uptake of iodine by the thyroid is examined.
- For euthyroid adult subjects, a between-days difference of 20% is concluded.
- This inherent variation decreases the precision of relative RAIU data.
- A critical effect size (CES/BMR) of 20% is proposed for benchmark dose analysis.

ARTICLE INFO

Article history:
Received 14 April 2016
Received in revised form 31 May 2016
Accepted 2 June 2016
Available online 3 June 2016

Keywords:
Thyroid
Radioiodine
RAIU
Intra-individual variation
Benchmark dose analysis
Benchmark response
Critical effect size
Perchlorate
TDI
Risk assessment

ABSTRACT

Potential adverse effects of chemical substances on thyroid function are usually examined by measuring serum levels of thyroid-related hormones. Instead, recent risk assessments for thyroid-active chemicals have focussed on iodine uptake inhibition, an upstream event that by itself is not necessarily adverse. Establishing the extent of uptake inhibition that can be considered de minimis, the chosen benchmark response (BMR), is therefore critical. The BMR values selected by two international advisory bodies were 5% and 50%, a difference that had correspondingly large impacts on the estimated risks and health-based guidance values that were established. Potential treatment-related inhibition of thyroidal iodine uptake is usually determined by comparing thyroidal uptake of radioactive iodine (RAIU) during treatment with a single pre-treatment RAIU value. In the present study it is demonstrated that the physiological intra-individual variation in iodine uptake is much larger than 5%. Consequently, in-treatment RAIU values, expressed as a percentage of the pre-treatment value, have an inherent variation, that needs to be considered when conducting dose-response analyses. Based on statistical and biological considerations, a BMR of 20% is proposed for benchmark dose analysis of human thyroidal iodine uptake data, to take the inherent variation in relative RAIU data into account. Implications for the tolerated daily intakes for perchlorate and chlorate, recently established by the European Food Safety Authority (EFSA), are discussed.

1. Introduction

Measurement of the uptake of radioactive iodine as a diagnostic tool for thyroid function testing (RAIU test) was introduced in the fifties of the previous century (Astwood and Stanley, 1947; Goodwin et al., 1951; Greer, 1951). As reliable methods for measuring thyroid hormones became available the diagnostic use of the RAIU test declined, but in recent years the test has been employed for examining the potential adverse effects of chemical substances on the human thyroid (Braverman et al., 2005, 2006; Greer et al., 2002; Hunault et al., 2007; Kunii et al., 2016; Lawrence et al., 2001, 2000). In the RAIU test, a quantity of radioactive iodide, usually sodium ^{131}I-, ^{132}I- or ^{123}I-iodide, is administered orally. At a specific time after administration, the fraction of the radioactivity absorbed by the thyroid is determined by measuring the locally

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http://dx.doi.org/10.1016/j.toxlet.2016.06.004

emitted radiation by means of a probe held near the anterior neck (Becker et al., 1996).

The normal range of values for the 24-h iodine uptake in euthyroid subjects is usually defined as 10–30% but may be as large as 15–50% in certain parts of the world (Becker et al., 1996; Franklyn and Shephard, 2000). In the Greer et al. study, the range of 24-h RAIU values before treatment was 9.8–33.7% (Greer et al., 2002). The rather large normal range has implications for studies into the potential effects of a chemical substance on the thyroidal iodine uptake in humans, because it reduces the discriminating power of a dose-response study with a standard design (several treatment groups and a control group). That is, the relatively large inter-individual variability in iodine uptake makes it difficult to distinguish a change in RAIU due to exposure to a substance when comparing group average values of exposed and unexposed subjects.

To account for the impact of inter-individual variability in RAIU in the human population, several researchers have used study designs in which subjects served as their own controls and where the effect measure is the change in RAIU value during exposure to a substance relative to the subject's pre-study value (Greer et al., 2002; Lawrence et al., 2001; Lawrence et al., 2000). However, this procedure does not account for intra-individual variability and implicitly assumes that the subject's pre-treatment value is constant during the study, and ignores the normal day-to-day variation in thyroidal iodine uptake. This omission becomes critical if the calculated relative differences are used for deriving a tolerable daily intake level for a substance, employing benchmark dose (BMD) analysis.

BMD analysis is recommended by regulators and other scientists to assist the determination of, or to establish acceptable limits for, exposure for chemical substances (Crump, 1984; EFSA, 2009; U.S. EPA, 2012). A BMD analysis essentially involves fitting a dose-response curve to the observed study data (often obtained at higher doses and response levels than would be desired in the human population) and then using the mathematical function describing that curve to predict the dose or level of exposure that would be associated with a minimum level of a physiological response considered adverse. The minimum level of a physiologically adverse response (e.g., a level of iodine uptake inhibition, a change in body weight, a change in the serum concentration of a hormone) is termed the benchmark response (BMR). Proper selection of a BMR is critical to the BMD analysis; the BMR must be a meaningful change, both in terms of statistics (is the degree of change described by the BMR distinguishable from background?) and biology (is the degree of change meaningful in terms of being on the margin of something physiologically adverse?).

BMD analysis was conducted for assessing the health risk of exposure to perchlorate by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2011 (FAO and WHO, 2011) and more recently by the Panel on Contaminants in the Food Chain (CONTAM) of the European Food Safety Authority (EFSA, 2014). Both expert groups established a tolerable daily intake (TDI) for perchlorate using data on thyroidal iodine uptake inhibition determined in the Greer et al. human volunteer study. JECFA selected a BMR of 50% for the inhibition of thyroidal iodine uptake, because this level of inhibition was not associated with changes in the levels of thyroid hormones or TSH following short-term and chronic exposure of healthy adults to perchlorate (Greer et al., 2002; Lamm et al., 1999; Lawrence et al., 2000; NAS, 2005). In contrast, the CONTAM panel posited that chronic adaptive changes in the thyroid to compensate for a sustained inhibition of the uptake of iodine could lead to thyroid disease, in particular in mildly to moderately iodine deficient people, even if thyroid function tests show no effect following short-term exposure to inhibitors. Based on this hypothesis, the EFSA panel selected 5% inhibition of the iodine uptake as the BMR in their BMD analysis of the Greer et al. data. The CONTAM panel also argued that 5% is the default BMR value applied for continuous data, although EFSA's guidance describes this default value in the context of animal studies, and indicates that health-endpoint-specific BMR values may be used based on statistical or toxicological considerations (EFSA, 2009). Largely because of this difference in BMR, the tolerable daily intakes established by JECFA and EFSA are different: 10 μg/kg bw/day versus 0.3 μg/kg bw/day, respectively.

Use of a default BMR value of 5% for change in RAIU does not appear consistent with the known variation in this parameter. Variation in RAIU measurement attributable to experimental errors is estimated to be ≤5% (Francois et al., 1958; Gomez Crespo and Vetter, 1966), but repeated measurements in euthyroid subjects (Francois et al., 1958; Hare and Haigh, 1955; Levy et al., 1959) revealed much larger differences between measurements in the same person. Francois et al. calculated a standard deviation of 15.3% for the relative differences of each of four 6-h RAIU measurements with the mean value of each subject (n = 17). The authors estimated that the physiological contribution to the observed intra-individual variation has a standard deviation of 14.4%, suggesting biological and/or environmental factors play a prominent role in the observed day-to-day variation of thyroidal iodine uptake. Irrespective of the cause of the variability, in order to decide what level of change is of toxicological relevance, the risk assessor needs to consider the normal variability for this endpoint in healthy individuals without known thyroid diseases. More specifically, when using the Greer et al. study for establishing a tolerable intake level for perchlorate, the inherent variation in the calculated IU inhibition due to the normal intra-individual inter-day variability in RAIU values in untreated subjects in the study population should be taken into account.

The present analysis was undertaken with the aim of establishing an appropriate BMR for the benchmark dose analysis of the inhibition of thyroidal iodine uptake in humans, in particular as determined in the Greer et al. study.

2. Materials and methods

Literature searches were conducted via MEDLINE (PubMed), and by searches on the Internet; the latest one in March 2016. Literature was selected primarily on the basis of the combinations of search terms 'thyroid', 'RAIU', 'radioactive', 'iodine/iodide' and 'variations' in the title or abstract. Publications cited in the selected articles were reviewed if considered appropriate. Only publications containing individual level RAIU data were included in the analysis. If data were only presented in graphical form, GetData Graph Digitizer (www.getdata-graph-digitizer.com) was used to retrieve data values. In the Greer et al. study, the 8-h and 24-h uptake of radioactive iodine was determined on several occasions. Several other studies were identified, in which 24-h radioactive iodine uptake was repeatedly measured in the same subjects, whereas no other repeated 8-h RAIU measurements were found in the literature. For this reason, we concentrated our analysis on available 24-h RAIU data.

As outlined in the introduction, in the Greer et al. study the effect of perchlorate on the thyroidal uptake of iodine was analysed by expressing RAIU values measured during treatment as a percentage of the pre-study RAIU value. To be consistent with this approach, we also analysed the untreated RAIU data obtained via the literature search using this approach, i.e., taking the first measurement collected as the baseline value:

$$\frac{|\text{first measure} - \text{second measure}|}{\text{first measure}} \times 100$$