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Critique of the ACGIH 2016 derivation of toluene diisocyanate Threshold Limit Values

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ABSTRACT

In 2016, the American Conference of Governmental Industrial Hygienists (ACGIH) lowered the 8-hr Threshold Limit Value - time-weighted average (TLV-TWA) for toluene diisocyanate (TDI) from 5 ppb to 1 ppb, and the 15-min short-term exposure limit (STEL) from 20 ppb to 5 ppb. We evaluated ACGIH's basis for lowering these values. It is our opinion that the ACGIH's evaluation of the evidence for occupational asthma and respiratory effects from TDI exposure does not fully integrate the results of all the available human and animal studies. We found that some studies reported occupational asthma cases at TWAs less than 5 ppb, but these cases were likely caused by peak exposures above 20 ppb. Advances in industrial hygiene have reduced peak exposures and the incidence of upset conditions, such as spills and accidents, in modern TDI facilities. Taken together, the human evidence indicates that adherence to the previous 8-hr TLV-TWA and 15-min STEL (5 ppb and 20 ppb, respectively) prevents most, if not all, cases of occupational asthma, and eliminates or reduces the risk of lung function decrements and other respiratory effects. While limited, the animal literature supports the human evidence and indicates that TDI-induced asthma is a threshold phenomenon. We conclude that ACGIH's decision to lower the TLV-TWA and STEL values for TDI is not adequately supported.

1. Introduction

Toluene diisocyanate (TDI) is an organic compound that is used to synthesize polyurethane foams. It has two isomers that are used commercially: 2,4-TDI (CAS: 584-84-9) and 2,6-TDI (CAS: 91-08-7). While most of the diisocyanate industry uses a mixture with a ratio of 80:20 for 2,4-TDI to 2,6-TDI, other commercial mixtures are available. TDI is an occupational allergen, or sensitizer, for which the two isomers appear to be of a similar potency (Shiotsuka et al., 2000). A sensitizer is a chemical that causes a substantial proportion of exposed people or animals to develop an allergic reaction after repeated exposure to it. The condition of being sensitized to a chemical is also called chemical hypersensitivity (OSHA, 2016). With proper precautions, however, TDI does not pose an appreciable risk of occupational asthma (OA) to workers.

The American Conference of Governmental Industrial Hygienists (ACGIH) is a non-governmental organization that assesses industrial hygiene health and safety issues and provides scientific guidance for government, academia, and corporate facilities. One of its primary tasks is developing Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) for use in workplace exposure monitoring. TLVs are airborne concentrations of chemical substances to which *nearly all* workers can be repeatedly exposed, day after day over a working lifetime, without adverse health effects (ACGIH, 2016). ACGIH derives TLV - time-weighted averages (TLV-TWAs) to protect against long-term exposures and short-term exposure limits (STELs) to protect against peaks in exposure. TLVs are not intended to represent fine lines between safe and unsafe exposures, but rather are intended to protect typical workers from adverse health effects. TLVs are based solely on health factors, and ACGIH acknowledges that it may not be economically or technically feasible to meet established TLVs or BEIs. ACGIH has developed TLVs for more than 700 chemicals, including TDI.

Non-allergenic chemicals each generally exhibit a no observed adverse effect level (NOAEL) or no observable adverse effect concentration (NOAEC), either of which can be used as the basis for a TLV. There is some support for the assertion that all sensitizers also have thresholds for an allergic response (see, for example, Cochrane et al., 2015; Dotson et al., 2015). However, the exact mechanisms and the exposure level associated with the threshold response can vary based on the conditions of exposure (particularly the level of “peak” exposures), individual susceptibility, and other potentially unknown factors, which can make the threshold difficult to determine (Dotson et al., 2015; ECETOC,

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2017). Prevention of sensitization in naïve individuals, rather than elicitation in previously sensitized people, is generally considered the more appropriate and protective health endpoint upon which to base an occupational exposure limit (OEL) (Dotson et al., 2015). While the derivation of STELs (protective of peak exposures) can be difficult for occupational allergens due to a lack of data (Dotson et al., 2015), it is generally thought that acute, peak exposures are important in the development of TDI-induced allergic OA (Ott et al., 2003; Sastre et al., 2003).

ACGIH developed its first TLV-TWA for TDI in 1959; since that time, the TLV-TWA and associated STELs have been revised numerous times. In 1959, the first TLV-TWA for the 2,4-TDI isomer was set at 100 parts per billion (ppb); it was quickly lowered to 20 ppb in 1961. From 1983 to 1998, the TLVs for 2,4-TDI were 5 ppb as an 8-hr TWA concentration and 20 ppb as a 15-min STEL. In 1998, the TLV-TWA was revised to include both the 2,4-TDI and 2,6-TDI isomers (individually or as a mixture). In 2006, ACGIH proposed lowering the 8-hr TLV-TWA and STEL to 1 ppb and 3 ppb, respectively. In 2015, ACGIH revised the proposal to an 8-hr TLV-TWA of 1 ppb and a STEL of 5 ppb; these limits were adopted in 2016 (ACGIH, 2016).

Below, we critique the methodology used by ACGIH to develop the current TLVs, including its interpretation of the evidence. We found that the methodology is unclear, as the revised TLVs do not appear to be based on any specific study or calculation. Also, while previous, substantial reductions in workplace TWAs led to a reduction in OA cases, particularly after 1980, ACGIH did not consider that the evidence indicates that maintenance of 8-hr average TDI TWA concentrations less than or equal to 5 ppb (*i.e.*, the previous 8-hr TLV-TWA) will result in very few, if any, new cases of OA. Our review of the evidence suggests that facilities maintaining previous TLVs have little risk of new cases of OA in their workers.

2. Human evidence

In the 1950s and 1960s, TWAs in TDI manufacturing and polyurethane foam plants, where exposures were most often reported as an 80:20 mixture of 2,4-TDI and 2,6-TDI, were as high as 60 ppb, with peaks up to 200 ppb during leaks, spills, and other upset conditions (see Adams, 1975; as cited in ACGIH, 2016, and Porter et al., 1975). By the 1970s, average airborne TDI concentrations had lowered substantially, mainly because of process controls and other technological advances. At that time, TWAs generally ranged from 1 to 10 ppb in TDI manufacturing units and 5 ppb in foam production units; peaks ranged from 20 to 40 ppb or higher (Ott et al., 2000, 2003).

Currently, TDI TWAs are even lower. In two recent studies, many TDI measurements were below the limit of detection (LOD) or very low (0.5 μg/sample[1] [Hon et al., 2017] and 0.1 ppb [Middendorf et al., 2017]). Hon et al. (2017) conducted an analysis of exposure over time in TDI facilities in Canada. Each sample was at least 15 min in duration, with an average of about 1–1.6 h; the maximum duration was 6 h. The authors reported a significant decrease in the risk of the TWA exceeding 5 ppb as the years progressed (i.e., early 1980s to the late 1990s) (Hon et al., 2017); however, other studies indicate that there is still variability across jobs and across different plants. For example, Brzeznicki and Bonczarowska (2015) surveyed polyurethane foam plants between 2002 and 2012 and reported maximum TDI-TWAs that ranged from less than the limit of quantitation (0.02 ppb) to 8 ppb among departments in one plant, while in another plant, the highest TDI TWA concentration in any area was 1.8 ppb. Similarly, in a study with over 2300 TWA and peak samples across three US TDI plants, Middendorf et al. (2017) reported that mean and 95th percentile TWAs did not exceed 5 ppb in one plant, but some mean and 95th percentile TWAs were above 5 ppb in specific areas of two other plants. Similarly, there were no exceedances of the STEL at one plant, but there were some exceedances in other plants, but only in specific job types (field operators and those working in loading). Despite the documented peak exposures, across all TWA measurements, however, the average was only 0.65 ppb.

The respiratory effects of occupational exposure to TDI have been extensively assessed in epidemiology studies. Many of the available studies are cross-sectional surveys (*i.e.*, disease and exposure were measured at one point in time), but there are also a few key longitudinal studies (*i.e.*, workers were followed over time). The most commonly reported effects in these studies are irritation (*e.g.*, of the eyes and nose), lung function decrements, and new-onset OA or exacerbation of existing OA. These studies showed that new cases of OA and other respiratory effects in TDI workers have declined substantially over time as the typical concentrations of airborne TDI have decreased (Ott et al., 2003). While the bases for the TLVs are OA, lung function decrements, and eye irritation, it appears that ACGIH relied most heavily on the studies of respiratory sensitization/OA (ACGIH, 2016).

Below, we critique ACGIH's interpretation of the available epidemiology evidence and compare it to our evaluation of the exposure concentrations and conditions associated with OA in TDI-exposed workers. Inter- and intra-individual variability in health and immune status preclude the identification of universally protective exposure levels in previously sensitized individuals. In addition, the available evidence more readily supports a threshold for induction (*i.e.*, new cases in workers not previously sensitized to TDI). Thus, our review specifically focuses on OA induction and the potential factors associated with recent declines in OA, as well as the association between TDI and lung function decrements. We focus on studies published since the TLVs were last reviewed in 2004, as well as longitudinal and other key studies that ACGIH cited in the documentation used to support lowering the TDI TLV-TWA in 2016. In contrast to ACGIH, we found that the human evidence does not support that the revised, lower TWA will result in a lower risk of new cases of OA or other respiratory effects.

2.1. Respiratory sensitization

The incidence of TDI-associated OA has declined substantially since the 1950s; longitudinal studies indicate that the rate was likely under 1% starting in the mid-1970s and has more definitively been < 1% since the 1980s (Ott et al., 2003). While it is difficult to determine the exact exposure scenarios required to induce or elicit OA from TDI exposure, the available studies demonstrate that peak exposures above the current STEL (20 ppb) are critical, even in workplaces with relatively low TDI 8-hr TWA concentrations. Older studies (*e.g.*, workers exposed in the 1960s-1980s) were more likely affected by very high peak exposures resulting from the more frequent occurrence of upset conditions, inadequate ventilation, and fewer other process controls. By contrast, while there may be short-term peaks in TDI concentrations in modern-day facilities, peaks are often much lower than the peaks that were greater than 20 ppb commonly reported in historical operations that have been more strongly associated with new cases of OA (Gui et al., 2014). It is important to consider that while TWAs are affected by peak exposures, the impact of these peaks is diluted. This is because, while TWA concentrations of a chemical are effectively raised by peak exposures, the magnitude of these peaks are effectively “dampened” due to averaging (ACGIH, 2017). Further, interindividual variability in exposure (TWAs and peaks) is particularly apparent in some of these studies. Thus, using TWAs to generalize exposure across individuals with widely varying exposure levels cannot provide information on the risk of OA at specific TWAs and peak exposures.

In its 2016 documentation, ACGIH indicated that several studies support the position that the new TDI TLV-TWA of 1 ppb and STEL of 5 ppb would further reduce the incidence of OA and associated

[1] The air concentrations corresponding to this LOD varied by plant, depending upon sample volume. Hon et al. (2017) did not present the ppb-equivalent range or data in which the conversion could be made for individual plants. All LODs were below the Action Level of 2.5 ppb.