

Frequency and Trends of Occupational Asthma Due to Toluene Diisocyanate: A Critical Review

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In recent years, occupational asthma has become the most frequent occupational lung disease in many countries. Reports and statements on the frequency of occupational asthma due to isocyanates are quite contradictory. In order to clarify the issue, a critical review of the medical literature of the past half century worldwide has been performed, with special emphasis on toluene diisocyanate (TDI) as the main representative of the isocyanate family. Nine longitudinal workplace studies of 2,751 persons under risk allow calculation of incidences of occupational asthma due to toluene diisocyanate. Annual incidences had repeatedly been above five percent before 1980, and have decreased to zero to 0.7 percent since 1980. There is a downward trend during the last half century that clearly parallels the downward trend of toluene diisocyanate exposure in some studies.

Prevalences of occupational asthma due to toluene diisocyanate can be estimated from 10 cross-sectional studies, based on 788 persons. Prevalences had repeatedly been above 10 percent before 1985, and have been mostly between zero and 10 percent in recent years.

Keywords Toluene Diisocyanate (TDI), Occupational Asthma, Incidence, Prevalence, Trends

In recent years, occupational asthma (OA) has become the most frequent occupational lung disease in many countries.⁽¹⁾ Among the many agents that may cause OA, the isocyanates (IC) have gained wide attention. As far as the frequency of OA due to isocyanates is concerned, the medical literature is quite contradictory: On the one hand, prevalences of up to 85 percent⁽²⁾ and increasing annual incidences⁽³⁾ of more than 10 percent⁽⁴⁾ have been reported, and isocyanate asthma has been considered the most common type of OA.^(5,6) On the other hand, declining numbers of isocyanate asthma⁽⁷⁻¹¹⁾ with prevalences and annual incidences down to zero percent^(2,12,13) have been observed, and isocyanate asthma has been shown to be much less common than OA due to flour, amines, platinum salts, and other agents.^(1,3,9)

For a long time, toluene diisocyanate (TDI) has been the main representative of the isocyanate family. This review, therefore, concentrates on OA caused by TDI (TDI-A).

METHODS

The frequency of OA can be derived from four sources: workforce-based studies, surveillance schemes, compensation statistics, and disease registers.⁽¹⁴⁾ The latter three usually treat the isocyanate family as an entity; besides, they are very often unaware of the number of persons at risk. Therefore, the frequency of TDI-A can be derived mainly from TDI-workforce-based health studies.

We carefully searched through our archives, which contain (to the best of our knowledge) the complete medical literature on IC health effects since the first publication in 1951. There have been many reports on lung function and immunology. However, data on the frequency of TDI-A are rare, often hidden, and incomplete. We finally selected nine longitudinal studies and 10 cross-sectional studies that allow the calculation of incidences (occurrence of new cases in a population over a time period) and prevalences (proportion of a population affected by disease at a certain time point) of TDI-A.

Some of these studies have been published by more than one paper; in such cases, the most relevant peer-reviewed final publication will be quoted here (e.g., references 15 and 16). For the calculation of incidences and prevalences, this review considers only those publications that contain information on OA exclusively due to TDI.

The decision whether or not a study should be included in this review was quite difficult in some cases because of insufficient or equivocal data. There are no absolute criteria for such a decision in "borderline" studies, and the decision, therefore, may remain somewhat subjective and debatable. However, in the results section of this review, relevant peculiarities of borderline studies will be addressed.

The calculated numbers for incidences and prevalences, too, are not unequivocal in some cases, depending on (1) the chosen size of the workforce (initial, average, or total size; consideration of the whole group or of subcohorts; inclusion or exclusion

of newcomers and leavers); (2) the chosen time period for the calculation of average annual incidences (whole study period or fractions thereof); and (3) the validity of the diagnosis "TDI-A" (suspected vs. proven cases).

As far as the size of the workforces in longitudinal studies is concerned, this review adopts the numbers upon which the individual author has based his calculation. Different use of any of the mentioned parameters may cause discrepancies between this review and others.

RESULTS

Incidence of TDI-Asthma and Trends

Table 1 lists the selected nine longitudinal studies in chronological order of their publication.^(12,15-22) The studies are based on a total workforce of 2,751 persons under risk, and they cover a 38-year time period from 1954 to 1992.

As can be seen, there are great differences between the average annual incidences of TDI-A. This is due to the following variables:

- Current and previous TDI exposure (cf²³)
- Cohort size and selection (e.g., inclusion or exclusion of persons with pre-existing bronchial asthma or atopy).
- Length of observation period (During short observation periods, a fluctuation of case numbers may play an undue role.)
- Validity of diagnosis—This review distinguishes between three degrees of validity:
 - "Self-reported, work-related symptoms," which may bear little relation to the clinical diagnosis,⁽¹⁴⁾
 - "MD opinion," which focuses on the subjective interpretation of personal and occupational history;
 - "Clinical evidence," which is corroborated by objective data such as spirometry, serial peakflow, immunological parameters, or inhalation challenge tests;
 - Current and previous TDI exposure⁽²³⁾; and
 - Cohort size and selection (e.g., inclusion or exclusion of persons with pre-existing bronchial asthma or atopy).

Some papers deserve specific comments. Woodbury⁽¹⁷⁾ mentioned two cases of TDI-A and five "possible cases" (the latter were not included here because of missing diagnostic details). The Adams study⁽¹⁹⁾ may have overestimated the incidence of TDI-A: Any employee who was reassigned to another production unit because of respiratory signs and symptoms was counted as a case of "TDI sensitization;" thus, it could have been difficult to distinguish acute irritant from asthmatic responses. Incidentally, the annual incidence rate of TDI-A was 18 percent for the first year of employment and 2.3 percent thereafter. The

study by Porter et al.⁽¹²⁾ is a good example of different annual incidences that can be calculated from the very same data: the average annual incidence of TDI-A for the whole 17-year study period is 0.9 percent. If we break up the study period into several fractions, the resulting average annual incidences are 1.1 percent for the period of 1957-1971, and zero percent for the period of 1972-1974 (see Table I), or steadily declining annual incidences from 2 percent in 1957 down to zero percent in 1972-1974 (see Figure 1).

Several reports with inconsistent results have been published on the Tulane study, which was conducted during 1973-1978. According to Butcher et al.,⁽²⁴⁾ the average annual incidence of "clinical sensitivity" was 1 percent, while Weill et al.⁽²⁵⁾ and Diem et al.⁽¹⁵⁾ reported 0.9 percent and 0.7 percent, respectively, as the average annual rate of "clinical TDI asthmatic reactors" per annum.

The differences are obviously due to (1) different criteria for the diagnosis of TDI-A and (2) differences in the size of the study population used for the calculations (inclusion or exclusion of newcomers and leavers). For this review, the Diem et al. figures⁽¹⁵⁾ have been used because this publication was the final one.

The paper by Omae⁽²⁰⁾ must be carefully interpreted. On one hand, it mentions six cases of "latent or subclinical asthma," that obviously had developed during long-term TDI exposure prior to the study. On the other hand, these cases remained "silent" during the two-year longitudinal study, with low TDI exposures, and no new cases of TDI-A were registered during the study period. Thus, a zero percent annual incidence of TDI-A must be calculated for the study period.

The Jones et al. study⁽²¹⁾ reported a total of 12 cases of TDI-A as observed during the study period: six were proven by specific inhalation challenge, and six were probable cases. However, all six proven cases had developed symptoms prior to the start of the study and were thus prevalent cases. We quote the six probable cases in this review, accounting for the very high medical standard of the study.

The largest longitudinal study has been conducted in the United Kingdom, and several reports have been published. We adopted the data supplied by the final Clark et al. paper.⁽¹⁶⁾ It should be noted that six of 18 cases counted as TDI-A had upper airway symptoms only, and that none complained of severe wheeze and breathlessness.

As can be seen, the average annual incidences of TDI-A had been as high as 2.7 to 5.5 percent in the early days of TDI production and use. Annual incidences have decreased to 0.3 to 0.7 percent since the late 1970s. Zero percent annual incidences have been observed.^(12,20) There is no obvious difference between TDI manufacture and flexible foam production. Most of the data come from the United States. There is no significant difference between the European study⁽¹⁶⁾ and the American studies.

Figure 1 illustrates the quoted annual incidences plotted against the time period of their observation. A general downward

TABLE I
Workplace data on the incidence of TDI asthma

Author	Cohort size (# of persons at risk)	Industrial process	Study type, observation period	Criteria for the diagnosis of TDI asthma	Comments	Average annual incidence (%)
Woodbury, ⁽¹⁷⁾ 1956	25	Flexible foam production	1.5 year retrospect., 1954–1955	MD opinion	Frequent spills	5.3
Williamson, ⁽¹⁸⁾ 1965	99	TDI research and development	1.5 year retrospect., 1962–1963	Clinical evidence	Frequent spills	2.7
Adams, ⁽¹⁹⁾ 1975	565	TDI manufacture	9 year prospect., 1961–1970	MD opinion and spirometry	Frequent overexposures	5.5
Porter et al., ⁽¹²⁾ 1975	200	TDI manufacture	17 year retrospect., 1957–1971 and 1972–1974	Clinical evidence	Declining incidence with decreased exposure	1.1 0
Diem et al., ⁽¹⁵⁾ 1982	277	TDI manufacture	5 year prospect., 1973–1978	Clinical evidence	Frequent pre-existing respiratory symptoms; 50% of asthma cases after major spills	0.7
Omae, ⁽²⁰⁾ 1984	106	TDI manufacture and research	2 year prospect., 1980–1982	MD opinion and spirometry	High attrition rate	0
Jones et al., ⁽²¹⁾ 1992	386	Flexible foam production	5 year prospect., 1982–1986	MD opinion		0.3
Clark et al., ⁽¹⁶⁾ 1998	780	Flexible foam production	5 year retrospect., 1981–1986	Self-reported symptoms		0.6
Ott et al., ⁽²²⁾ 2000	313	TDI manufacture	25 year retrospect., 1967–1980 and 1980–1992	Mostly MD opinion	Declining incidence with decreased exposure	1.8 0.7

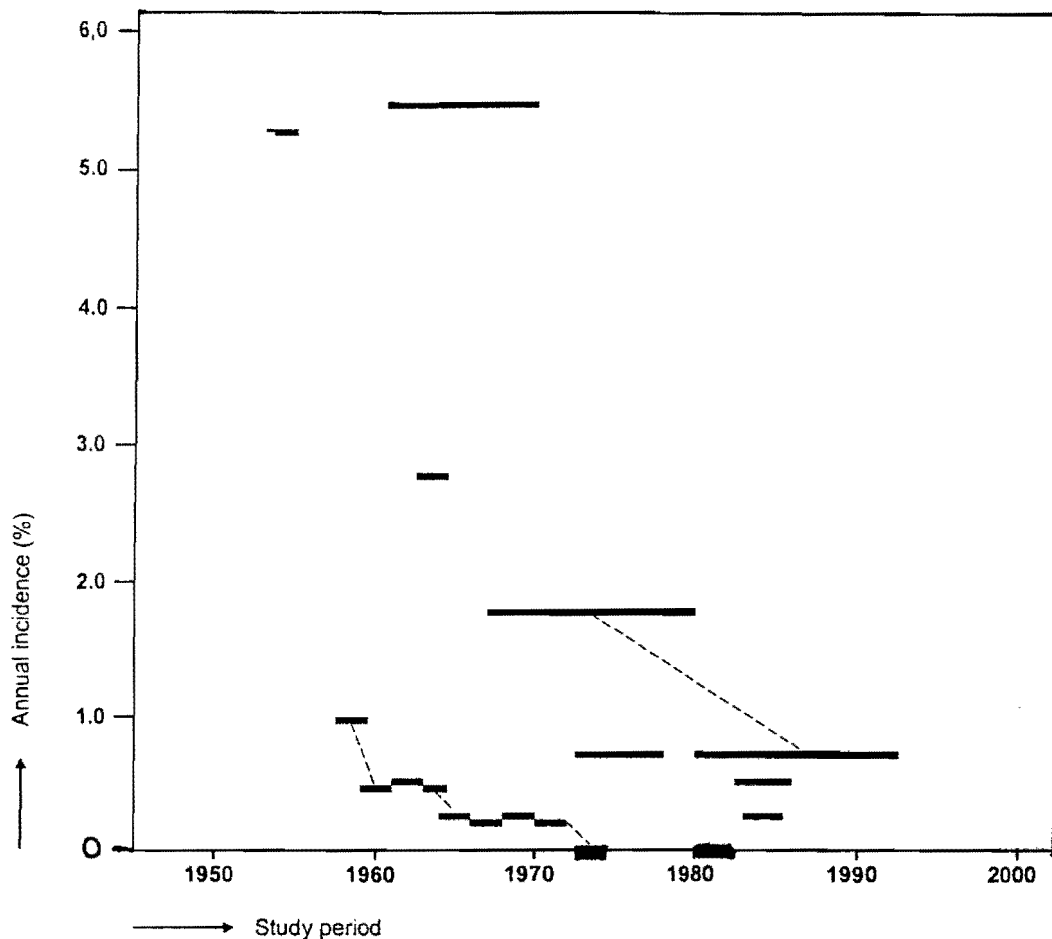


FIGURE 1
Reported annual incidence of TDI asthma (1954-1992).

trend over the past half century is obvious, in spite of the fact that the average annual incidence during a longitudinal study period has often been plotted as a horizontal bar for the whole study period. The downward trend is quite conspicuous in the two studies that estimated the incidence of TDI-A within a certain workforce for different time periods.^(12,22)

Prevalence of TDI-Asthma and Trends

In the medical literature worldwide, 10 relevant cross-sectional studies have been found that allow the calculation of prevalences of TDI-A. The publications report on a total workforce of 788 persons at risk, and they cover a 38-year period from 1954-1992. Table II lists these studies in chronological order of their publication.^(2,13,26-33)

The validity of most of these studies is rather limited: small cohorts prevail,^(2,13,26,27,30,32) some cohorts are highly selected,^(26,27) some represent survivor populations,^(27,28) several studies rely on self-reported symptoms,^(2,29,31) the industrial processes are quite heterogeneous, and TDI exposures vary considerably.^(2,13)

Some studies require specific comments. Two Asian studies^(2,13) report prevalences of TDI-A among very small sub-cohorts with quite high TDI exposures (up to 112 ppb); at these TDI concentrations, it should have been difficult to distinguish between irritant and allergic reactions without confirmation by specific inhalation challenge.

The study by White et al.⁽²⁸⁾ is difficult to interpret. Thirteen out of 68 persons (19%) reported asthmatic symptoms prior to the use of the TDI-laminated nylon foam fabric. Positive inhalation challenges by handling the TDI-laminated nylon fabric were observed in three persons, and a positive exposure test during painting a TDI varnish was observed in one person. All these challenges were performed with unknown concentrations; thus, it should have been difficult to distinguish between reactions due to nonspecific bronchial hyperreactivity and those due to true TDI-A. This review quotes the authors' assumption that TDI-A developed in one subject.

In view of all the quoted limitations, it is not surprising that the reported prevalences of TDI-A scatter over a wide range between zero and 85 percent. During the past 15 years, measures of prevalences between zero and 10 percent have been observed

TABLE II
Workplace data on the prevalence of TDI asthma

Author	Cohort size (# of persons at risk)	Industrial process	Criteria for the diagnosis of TDI asthma	Comments	Prevalence (%)
Bruckner et al., ⁽²⁶⁾ 1968	26	TDI manufacture	Clinical evidence	Selected cohort	19.4
Franzinelli et al., ⁽²⁷⁾ 1978	66	Foam production	Clinical evidence	Survivor population	3.0
White et al., ⁽²⁸⁾ 1980	147	Sewing laminated nylon	MD opinion	Frequent pre-existing respiratory symptoms	0.7
Kido, ⁽²⁹⁾ 1983	87	Lacquer varnishing	Self-reported symptoms		16.0
Belin et al., ⁽³⁰⁾ 1983	48	Foam production	Clinical evidence	Survivor population	0
Venables et al., ⁽³¹⁾ 1985	221	Foam coating of steel	Mostly self-reported symptoms		9.5
Wang et al., ⁽²⁾ 1988	38	Adhesive tape production	Self-reported symptoms	Small subgroups with mean exposures of 12, 21, and 47 ppb TDI	0 38 85
Huang et al., ⁽¹³⁾ 1991	48	Varnish application	MD opinion	Small subgroups with mean exposures of 15, 44, and 112 ppb TDI	0 15 27
Lee-Phoon, ⁽³²⁾ 1992	26	Foam production	MD opinion		0
Kim et al., ⁽²⁶⁾ 2000	81	Paint application	Clinical evidence		9.9

at workplaces with mean TDI exposures below 15 ppb. A strong correlation between the prevalence of TDI-A and TDI exposure has been suggested by two studies.^(2,13)

DISCUSSION

This review analyzes the results of studies that are quite heterogeneous in regard to population, validity of TDI-A diagnosis, industry branch, and TDI exposure. The picture is irregular and laden with inaccuracies and bias, but it is the best that can be done with the information currently available.

The presented data show an obvious downward trend of the incidence of TDI-A over the past half century. The search for the causes of this development may give clues to better prevention. Several reasons seem possible. The downward trend of TDI-A correlates closely with the downward trend of TDI exposure.^(12,22) Reduced TDI exposure, therefore, appears to be of prime importance. An increasing tendency toward earlier removal of persons with workplace-related respiratory symptoms could theoretically play a role, but there is no indication of such a tendency. A reduction of the population at risk (due to dismissals in times of economic recession) would lead to fewer new cases; the incidence, however, (as the ratio of both entities) would remain unaffected. Reduced TDI manufacture and use as a causal factor can be ruled out. The worldwide production of TDI has steadily increased during the past half century.⁽³⁴⁾

The prevalence of TDI-A has also been addressed in this review because this metric has played an important role in past discussions. Certainly, "prevalence" is the traditional metric for the frequency of a disease within a population. However, for the estimation of the frequency of OA, this metric is now considered

less reliable because, on one hand it registers asthma cases that have remained at the workplace for years, and on the other hand it fails to register those cases that have left the workplace.

It is interesting to note that the downward trend of TDI-A is not an isolated phenomenon. According to general surveillance schemes, compensation statistics, and disease registers, the annual case numbers of OA due to all types of isocyanates also show a downward trend in most countries during recent years,⁽⁷⁻¹¹⁾ in spite of steadily increasing production and use of all isocyanates.⁽³⁴⁾ The regional distribution, however, varies. While isocyanates as a cause of OA prevail in some North American states, the United Kingdom, Canada, and New Zealand,^(7,14,35) they rank far behind flour, animal dander, amines, platinum salts, and other agents in Germany, Switzerland, and Finland.⁽⁸⁻¹⁰⁾ These differences are likely due to (1) different types and sizes of regional industries with different standards of working practice and (2) differences in legal requirements, sources of reports, referral patterns, and diagnostic criteria.⁽¹⁴⁾

CONCLUSIONS

The published data are not easy to interpret because of a great number of variables. Cautious analysis leads to the conclusion that the incidence of TDI-A shows a clear downward trend in the United States and Europe during the past half century. Annual incidences of TDI-A worldwide have oscillated between zero and 0.7 percent during the past two decades. The prevalence of TDI-A has been reported to range between zero and 10 percent during the past decade at workplaces with mean TDI exposures below 15 ppb.

RECOMMENDATIONS

Future research should be directed toward assessing the frequency of OA due to other specific isocyanates, such as methylene diphenyl diisocyanate and hexamethylene diisocyanate prepolymers, which are quite different from TDI in regard to industrial use and health risks. This would help to detect clusters of OA, which could then be tackled by specific preventive measures.

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