MDI and TDI: Safety, Health and the Environment.

A Source Book and Practical Guide

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errors or omissions therein. While the text discusses certain of the manufacturing, handling,
environmental, medical and other aspects of the diisocyanate industry, it does not purport to
be, and is not, a comprehensive guide thereto.*

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3   Health

Health aspects of MDI and TDI have been subject to intensive research, in terms of both human and animal toxicological studies. It has even been suggested that TDI has been subject to more intensive study than any other chemical. One important reason is that diisocyanates may cause asthma in sensitive individuals at extremely low concentrations. MDI and TDI are included in diverse regulatory listings of dangerous chemicals because of this factor. Asthma is a major component of occupational respiratory disease in many industrialized countries, and diisocyanates (including aliphatic diisocyanates) have been implicated in a significant percentage of cases.

There is a significant body of evidence to indicate that workers who are exposed to less than 20 parts per billion (ppb) of MDI or TDI have a very low risk of developing respiratory symptoms or occupational asthma, or of becoming sensitized. Respiratory symptoms may occur in some subjects who are especially sensitive when they are exposed to less than 20 ppb, a ceiling concentration limit adopted by many regulatory authorities. Thus, there is a real need to be vigilant in reducing exposure levels in the workplace by appropriate training of personnel and by regular medical surveillance of those potentially at risk, and above all by reducing isocyanate exposure to levels well below regulatory limits, by the use of engineering controls.

Whilst MDI and TDI can cause significant health effects at very low concentrations, most exposed workers will not suffer ill effects from their exposure. In that respect the evidence of one of the authors (an experienced physician) who has focused on diisocyanate health effects is pertinent.

A physician's summary

When I took over medical responsibilities for the large diisocyanate division in my former company many years ago, I read all the available medical literature on diisocyanate effects. I was thrilled, anticipating most spectacular activities. When I had to give a presentation on diisocyanate health effects to an industry panel, I obviously shocked everybody by my horror scenarios and I was asked how on earth anyone could work with such hazardous chemicals. The passage of time and growing personal experience modified the wisdom of books and articles, and I realized that my job was not so spectacular at all. Health effects due to diisocyanates were rare; they had to be searched for. It was this search (including the investigation

> *of causes) which made my job so interesting. And now, after two decades of such activities, I am convinced that one can handle diisocyanates safely if all necessary precautions are taken.*
>
> Professor Dr med. W F Diller

The first part of this text deals with the results of human experience, commencing with a commentary on first aid. The second part of the text deals with experimental toxicology, and the relationships between the results of these studies. Finally, there are appendices that give a practical scheme for the diagnosis of diisocyanate asthma and a medical survey form which has been used with diisocyanate workers. No attempt has been made to be comprehensive in recording all the available literature, as it is so extensive. However, it is hoped that all significant aspects of the relevant topics have been captured.

Perspective on immediate effects following over-exposure

Main threat: inhalation

Responses to over-exposure to airborne MDI or TDI may vary widely from mild irritation of the airways to more severe effects, even to bronchospasm. In extremely rare cases, particularly with individuals who have previously become sensitized to the diisocyanates, the effects may be life threatening. Long-lasting respiratory effects may develop following repeated over-exposure to MDI or TDI.

Other threats: skin and eye contamination, swallowing

There is no indication whatever that these are life threatening. Prompt treatment will be necessary to alleviate the symptoms and minimize damage.

First aid procedures

In all situations involving MDI or TDI where first aid is necessary, the principles of general first aid in accident situations should be followed. The persons involved should be moved from further immediate risk, and relevant first aid should be given to treat any physical injury not directly connected with exposure to diisocyanates.

Rescuers and first aiders should take care to protect themselves from exposure, especially if the subject is heavily contaminated. MDI and TDI have poor olfactory warning properties so first aiders may not be aware that they are being exposed to concentrations well above the short-term exposure limit. Prior to approach to an incident they should put on air-supplied breathing equipment. They will also need to wear gloves and chemical protective clothing.

The following guidance to first aiders is for the purpose of addressing problems associated with short-term over-exposure to MDI or TDI.

MDI or TDI: First aid

Breathing difficulties due to vapour, aerosol or MDI dust

- The person affected should be moved from risk of further exposure and made to rest.
- Obtain medical attention immediately.
- The onset of symptoms may occur several hours after exposure has taken place.

Eye contamination

- Flush the eyes immediately with the contents of several sterile eye wash bottles or copious amounts of tap water. Then remove contact lenses, if present and easily removable, and continue eye irrigation for not less than 15 minutes.
- Obtain medical attention.

Skin contamination

- Wash off thoroughly with large amounts of water and then wash well with soap and water.

Swallowing

- Do not induce vomiting.
- Wash out the mouth with water.
- The person affected should be made to rest.
- Obtain medical attention.

Notes for guidance of physicians

- MDI and TDI are respiratory irritants and potential respiratory sensitizers. There are no specific antidotes and treatment is essentially symptomatic for primary irritation or bronchospasm.
- MDI and TDI have very low oral toxicity.
- Post-incident checks are needed.

Commentary on first aid procedures

Removal from exposure

Both MDI and TDI have very low vapour pressures and do not evaporate quickly. However, they can give sufficiently high airborne concentrations to cause major acute breathing problems to those affected and to first aiders. It is important that all those involved move from the exposure source. Affected

clothing should be removed to prevent further exposure, and should be placed in a plastic bag or other impervious container to await decontamination or safe destruction. An affected person should be kept warm if a shower has been used to remove contamination.

Breathing problems

BREATHING DIFFICULTIES DUE TO VAPOUR, AEROSOL OR MDI DUST

The person affected should be moved from risk of further exposure and made to rest. Obtain medical attention immediately. The onset of symptoms may occur several hours after exposure has taken place.

The main exposure risk is to the respiratory tract. The effects may be immediate or delayed (for example, coughing or wheezing, commencing at night), sometimes making the relationship to the workplace over-exposure difficult to recognize. In *mild cases* there may be slight irritation of the nose and throat. There may be dryness of the throat, wheezing, tightness of the chest, coughing or shortness of breath. In *severe cases* the victim may suffer acute bronchial irritation with difficulty in breathing, or even bronchospasm.

The treatment is essentially symptomatic. Those affected should have their clothing slackened, should be kept warm and be given oxygen if there are severe breathing difficulties. A physician may consider administering a bronchodilator in some cases. If the situation becomes life threatening and breathing stops, artificial respiration should be applied.

Eye contamination

EYE CONTAMINATION

Flush the eyes immediately with the contents of several sterile eye wash bottles or copious amounts of tap water. Then remove contact lenses, if present and easily removable, and continue eye irrigation for not less than 15 min. Obtain medical attention.

Permanent effects from eye contamination are rare. **Care must be taken not to damage eyes by excessive flushing.** A low pressure eye fountain or other source of low pressure water is suitable. Washing should be continued until the stinging of the eyes has been relieved. During this period the patient should be encouraged to move the eyes, from side to side and up and down, to aid dilution. The minimum period of flushing should be 15 min and, if possible, the water should be lukewarm. Some assistance will normally be necessary to hold the eyelids apart, so that the diisocyanate or diisocyanate mixture is efficiently removed.

After first aid treatment, the patient should be seen by a physician or at the local hospital, since additional treatment may be necessary. A physician may wish to apply a suitable eye medication.

Skin contamination

SKIN CONTAMINATION

Wash off thoroughly with large amounts of water and then wash well with soap and water.

Remove contaminated clothing so that further skin contamination is avoided. The clothing that has been removed should be placed in an impervious bag, prior to decontamination. Skin contamination may cause irritation and, in a few cases, skin sensitization. If the diisocyanate was hot, some treatment for local thermal burns may be necessary.

The skin should be wiped with absorbent material to remove as much diisocyanate as possible, and the contaminated absorbent put into an impervious bag for later decontamination or disposal. The skin should then be washed with soap, or liquid soap, and warm water. For extensive contamination, a warm shower may be advisable. Proprietary skin cleaning agents should be used only if they have gained approval from hygiene studies. Recent research work has suggested that polypropylene glycol or corn oil may be more efficient at removing MDI from the skin than soap and water. Cleaning soon after exposure is important. **Organic solvents such as acetone, toluene or chlorinated hydrocarbons should not be used under any circumstances**, as they may promote absorption of the diisocyanates through the skin and into the body. If cold water is used to wash with, TDI and MDI may become more viscous, making cleaning more difficult. Very cold water may cause TDI to crystallize.

If a reacting polyurethane mixture solidifies on the skin or in the hair, it can usually only be removed mechanically.

Swallowing

SWALLOWING

Do not induce vomiting. Wash out the mouth with water. The person affected should be made to rest. Obtain medical attention.

There have been few reports of MDI or TDI being swallowed. Oral toxicity appears to be very low, in conformity with animal test results. Medical attention should be obtained immediately. No significant adverse effects are anticipated following ingestion. People who have ingested diisocyanates should be sent immediately to hospital with a copy of the relevant material safety data sheet(s). Medical staff may recommend inducing vomiting. **Induction of vomiting is not a first aid procedure and should be carried**

out only in hospital or when the medical benefits have been carefully taken into account by qualified medical practitioners. Some authors recommend giving the patient water or milk to drink; others recommend giving activated charcoal as an aqueous slurry within the first hour in patients who are awake and have a protected airway. Others recommend that nothing be given by mouth.

Post-incident checks

Those involved in incidents should be made aware that respiratory symptoms may be delayed or may increase over several hours. If symptoms develop, medical advice should be sought. The physician should monitor the patient for respiratory distress. If a cough or difficulty in breathing develops, the patient should be evaluated for respiratory tract irritation, bronchitis or pneumonia. The supplier or producer of the chemicals should be advised of any unusual or severe problems that are noted.

Human health: the medical background

A physician's experience

A medical officer in charge of workers handling diisocyanates may encounter a multitude of scenarios with or without links to diisocyanate exposure. Table 3.1 summarizes some situations which may occur prior to work with diisocyanates.

Table 3.1 **At pre-placement examination to assess fitness to work with diisocyanates.**

Problem	Medical consideration	Medical action
Recurrent hay fever	Common hay fever should not pose any problems to those working with diisocyanates; however, in severe cases with accompanying exertional dyspnoea (breathlessness) subjects may suffer from nonspecific bronchial hyperresponsiveness.	Clarify severity of hay fever; perform test for nonspecific bronchial hyperresponsiveness; assess probable future diisocyanate exposure; explain health risks and the need for careful medical surveillance, as well as for strict respiratory protection requirements.
Recurrent or chronic eczema	Subject generally not suited for work in the chemical industry, because many chemicals can cause exacerbation, though MDI and TDI are only slight skin irritants.	Explain increased risk for the skin, especially when involved in production processes. Stress the need for careful skin protection.

Table 3.2 **At medical surveillance examination or at office consultation.**

Problem	Medical consideration	Medical action
Influenza	Alveolitis (rare) due to diisocyanates, or true influenza?	Appropriate treatment. Detailed history. If suspicion of alveolitis arises, further diagnostic measures become necessary (lung function, immunology); eventually referral to specialist centre for final diagnosis.
Excess lung function decrement	Is this due to smoking, or general pulmonary disease, or diisocyanate exposure?	Detailed history, immunological tests, further close surveillance, examination of equally exposed co-workers.
Variable obstructive airways disease	Nonspecific chronic bronchitis or diisocyanate asthma?	Detailed personal history including smoking habits; lung function tests before and after administration of bronchodilators; serial peak flow measurements; immunological tests; close surveillance.
Irritation of eyes and upper respiratory tract	Transitory response to over-exposure with diisocyanates or other irritants? Is there the threat of ensuing reactive airways dysfunction syndrome (RADS) due to gross diisocyanate spillage or diisocyanate asthma?	Appropriate treatment of signs and symptoms. Repeated measurements of lung function, including tests for nonspecific bronchial hyperresponsiveness. Otherwise, referral to special centre for clarification.
Asthmatic attack	Underlying diisocyanate asthma or non diisocyanate asthma or nonspecific bronchial hyperresponsiveness?	Appropriate treatment. After regression of attack, further diagnosis in specialized centre. If diisocyanate asthma, no further exposure. Relocation of employee.
Vague complaints of exertional breathlessness	Normal ageing, or lack of fitness, excessive smoking or 'multiple chemical sensitivities' condition or the beginning of diisocyanate asthma?	Detailed history (including psychological aspects), serial peak flow measurements, immunological tests, further surveillance.
Blurred vision, blue haze.	Corneal oedema (tissue swelling) from tertiary aliphatic amine catalysts or other irritants?	Appropriate treatment, referral to ophthalmologist.
Skin problems	Diisocyanate origin or other cause?	Skin tests, referral to dermatologist.
Questions about risk of pulmonary cancer or coronary heart disease	Mortality studies in England, Sweden and the United States have shown no risks to individuals exposed to TDI and MDI.	Explain, reassure.

From time to time, workers who are potentially exposed to diisocyanates may be seen by a physician who will wish to understand whether diisocyanates are involved in the medical problems presented. Table 3.2 summarizes some possible situations that may arise.

A physician suspecting that diisocyanates are the cause of a medical problem with a patient should, when possible, advise the workplace management so

that suitable precautionary and/or preventative measures can be considered to minimize recurrence of the problem, for example, by improving ventilation or use of suitable protective clothing.

How are the effects of chemicals on health studied?

In vitro: in a test tube or an artificial environment.
In vivo: in a living system.

During the last four decades a systematic approach has evolved to the study of the health effects of chemicals. The approach consists of a combination of observations of the effects of chemicals on people, and studies in laboratory animals and *in vitro* test systems such as isolated enzymes. The complete body of knowledge on the potential health effects of chemicals is therefore derived by considering both sets of information as they build up, and this has been the case for the diisocyanates MDI and TDI. The observations in humans have highlighted a number of specific effects and the prevention of these effects has formed the basis for the evolution of the handling practices for diisocyanates, which have been steadily improved during this time. The basic experimental toxicology programmes have revealed a number of potentially adverse effects of diisocyanates to humans. The programmes have also indicated that MDI and TDI will not cause many of the adverse effects which other chemicals, whether natural or synthetic, have been shown to cause.

Observations in humans have the obvious advantage that the results are directly applicable to the species of concern, that is the human. The disadvantages of relying entirely on observations in humans are that, as most exposures to the chemicals are at relatively low concentrations, it is often not possible to obtain precise exposure data and that, in many exposure environments, there may be unmeasured confounding factors. Most experimental observations are limited to those which do not interfere with the well-being of the person being examined. Accidental over-exposures, usually to unknown concentrations of chemicals, may occur from time to time, and the physicians' reports on these cases can add usefully to the available information. Nevertheless, the time needed to draw accurate conclusions from human data can often be long.

The advantages of experimental toxicology are that exposure conditions can be manipulated and confined to the agent in question and that high exposures can be used. More invasive assessments can be used and experimental programmes can be performed within a shorter period of time. However, the major disadvantage is that the evidence must be extrapolated to humans. Certain conditions in man, such as asthma, are only incompletely reproducible in animals. Furthermore, anatomy, physiology and metabolism are different in different animal species, sometimes making meaningful extrapolation of animal test results to man particularly difficult. Consequently, both sets of information have to be considered together. Often observations in animal studies have led to specific investigations in humans and sometimes the reverse has been the case.

With diisocyanates, the rationale has worked in both directions, with experiments in animals leading to specific observations in humans, and observations in humans leading to mechanistic work using experimental animals to interpret and explain the results. This part of the book describes the body of evidence which has arisen from human observation and the underpinning scientific information derived from experimental toxicology. For convenience, the material has been organized with the human observations in one section and

the experimental toxicology in another section. However, it must be stressed that to determine the overall picture of the potential effects of diisocyanates on health, all of the evidence and its weight has to be considered and should be borne in mind by the reader.

Effects on the eyes

Vapours, aerosols or splashes of MDI or TDI may be irritant to the eyes.

In controlled experiments with volunteers the following thresholds for acute irritation of the eyes resulting from exposure to TDI vapour have been detected (Henschler, 1972).

80 ppb	2,4-TDI (30 min)	mild conjunctival irritation
80 ppb	2,6-TDI (30 min)	moderate conjunctival irritation
50 ppb	65/35 TDI (30 min)	slight conjunctival irritation (delayed some minutes)
100 ppb	65/35 TDI (30 min)	significant irritation
270 ppb	65/35 TDI (1 min)	burning sensation
500 ppb	65/35 TDI (30 min)	lachrymation
1300 ppb	65/35 TDI (10 min)	severe lachrymation

Conversion factors for vapour
TDI vapour: 1 ppb = 0.0072 mg/m^3.
MDI vapour: 1 ppb = 0.0104 mg/m^3.

No controlled experiments have been published for MDI. However, field observations are available. Irritation of the eyes, and also of the nose and throat, has been noted in workers exposed to MDI aerosol concentrations of 0.26 mg/m^3 (with additional exposure to irritant levels of styrene vapour) (Bodner *et al*., 1974). Bloodshot eyes were observed in polyurethane workers exposed to unknown concentrations of MDI (Hassman, 1973) and conjunctivitis with lachrymation was noted in another group of MDI foam workers (Lutier *et al*., 1970). Splashes of polymeric MDI into the eyes have caused transient inflammation of the eyelids and eye membranes, blepharo-conjunctivitis (Bertrand *et al*., 1984), and transient dilation of the pupils and impaired visual accommodation (Augustin and Göbbels, 1992).

As with other irritating chemicals, TDI splashed into the eye causes conjunctivitis and corneal oedema (tissue swelling). Blurred vision with ocular 'blue haze', which has been repeatedly encountered among workers engaged in the production of polyurethane foam who had no direct TDI eye contact, has been convincingly shown to be due to vapours of tertiary amine catalysts and not to TDI (Potts *et al*., 1986; Dernehl, 1966). Animal experiments on irritation to the eye by liquid MDI and TDI are in accord with human experience.

Effects on the skin

Acute dermatitis from MDI or TDI results from either massive skin contamination or a hyperresponsiveness of the skin. Chronic contact

dermatitis has only been observed as a consequence of very poor occupational hygiene. Both MDI and TDI thus appear to be very weak human skin irritants or sensitizers.

References on skin irritation
Lenaerts-Langanke (1992);
Bertrand *et al*. (1984); Lutier
et al. 1970.

Some citations on skin sensitization
Bernstein *et al*. (1993); Baur
et al. (1992); Estlander *et al*.
(1992); Fregert (1967);
Liden (1980).

See *Skin Diseases* detailed
cases in *Further reading*.

Patch-testing: the test
material is applied to the
surface of the skin and is
kept covered for the
duration of the test. Prick
testing: the test material
is applied intradermally
by a needle or syringe.

Skin problems from contact with MDI or TDI are rare in practice, and if they do occur they are usually due to inadequate occupational hygiene giving rise to extensive skin contamination with diisocyanates, solvents and additives used in polyurethane formulations. Prolonged exposure may lead to skin irritation or skin sensitization. Similar effects have been noted in animal toxicology studies. Cases of acute skin irritation have been observed occasionally in mines when MDI has been used for rock consolidation, and in other applications.

Occasional skin sensitization by MDI with resulting eczema or urticaria (skin rash with wheals) has been corroborated by skin tests. Moroni *et al*. (1985) observed one case of contact dermatitis and two cases of urticaria due to MDI, and seven cases of dermatitis due to TDI among a total of 1400 patch-tested occupational skin conditions. A systematic study was carried out by Rothe (1976) on 12 workers with folicular eczema due to MDI. Other well-documented single cases have also been described.

Cross-reactivity between MDI and methylenediphenyl diamine (MDA) is a common feature (von Gailhofer and Ludvan, 1989). A positive MDA patch-test often seems to be just a marker for skin allergies due to *para*-amino compounds. For example, a man who had never worked with diisocyanates developed dermatitis on the left wrist where he was wearing a watch strap made of MDI-based polyurethane. The patient exhibited a positive patch-test to the plastic strap and to MDA, but not to MDI. Further technical inquiry revealed that the plastic strap contained a *para*-amino compound as an anti-ageing agent (Walber, 1990, personal communication). In another case, a nurse handling a fibreglass-reinforced orthopaedic cast made from an MDI-based polyurethane developed dermatitis on hands and arms. Patch-testing showed that this was due to MDA and not to MDI. It was hypothesized that some of the MDI produced MDA on treatment of the rolls of the MDI casting tape with water (Bruynzeel and van der Wegen-Keijser, 1993).

Only a few detailed cases of skin diseases due to TDI are to be found in the medical literature. These cover acute dermatitis and chronic contact dermatitis or eczema. A few more anecdotal cases (including urticaria) have also been reported. The usual locations affected were hands, forearms, and faces. In some cases, the causal relationship with TDI has been proved by positive skin patch-testing. Cross-reactivity with other diisocyanates and related amines was observed occasionally. Cases of dermatitis have been reported, however, in which there were negative patch-test results to TDI but positive patch-tests to related amines or tertiary amine catalysts (Rothe, 1976), so that the causal relationship with TDI appears to be questionable in these cases. Careful skin testing with all the relevant occupational agents proved that TDI was not responsible in the case of a printer's contact dermatitis which indicated to be caused by a polythiol additive (Malten, 1979). Range-finding for patch-testing is essential, since in one case testing with 0.1 % TDI solution was negative, whilst a 0.5 % solution gave a positive test result (von Peschel,

1970). In normal subjects without previous diisocyanate contact, patch-testing with TDI solutions up to 10 % in strength caused no reaction, whilst concentrations between 10 and 20 % produced slight transient reddening. Patch-testing with diisocyanates should be undertaken only after careful consideration of the possible risks. Acetone or petrolatum are the recommended solvents for patch-testing. What role, if any, skin contact of diisocyanates plays in the development of respiratory sensitization is still under debate. Cured polyurethane foams were without effect on the skin in studies conducted by Dernehl (1966) and Zapp (1957).

Effects when swallowed

Both MDI and TDI have very low acute oral toxicities.

Inhaled material may be transferred to the gastrointestinal tract during the natural clearing of the respiratory tract (see below). However, only trace amounts would be expected to be swallowed. Therefore, it is widely accepted that oral uptake is not a relevant route of human occupational exposure for MDI or TDI. Animal studies have demonstrated very low acute oral toxicities for MDI and TDI. Understandably, there are almost no human data. However, there is a report of a suicide attempt by a man who drank 30 ml of a two-component MDI system for the manufacture of a polyurethane. A large lump of foam was found in his stomach and was removed surgically. No signs of illness were observed subsequently (Schmauss *et al*., 1982).

Effects on the respiratory tract

In the workplace airborne MDI or TDI may be present as vapour, in the form of aerosols, or adsorbed onto substrates as inhalable dusts. They may also be present as components in reacting polyurethane systems, which in some instances may be found as droplets.

Penetration of MDI or TDI into the respiratory system
Very small particles of a solid, or very small droplets of a liquid, can form relatively stable dispersions in a gas. These particles (aerosols) are of such a small size that they cannot be seen by the naked eye, even when in concentrations that may cause biological effects.

Aerodynamic diameter: the diameter of a unit sphere having the same settling speed (under gravity) as the particle in question, whatever its shape and density.

Aerosols will normally have individual particles of a range of sizes. Aerosol particles do not behave exactly like the surrounding air. Because they are denser than air they can settle out. The bigger the particles, the less gas-like in their flow behaviour they become and the more they tend to settle. The particle size (*aerodynamic diameter*) determines how far a particular particle will penetrate into the human respiratory system once inhaled. Aerosols of average particle diameter up to about 5 μm are respirable and can pass into

Figure 3.1 **Particulate aerosol inhalation curves**

the lungs like gases, whereas larger aerosols (up to $50\,\mu\text{m}$ in diameter) have less capability to penetrate the respiratory system (Figure 3.1).

Aerosols may be produced in a workplace in which polyurethanes are made using MDI or TDI, or in some situations in which the diisocyanates are being heated. Spraying is a particular operation in which aerosols can quite easily be formed. Very small particles may also be formed when polyurethanes are cut, shaped or subjected to grinding operations. In some situations the particles may contain adsorbed diisocyanates. Such aerosol particles are carried in dispersion in the surrounding air and can be breathed in unless suitable precautions are taken. Cartridge respirators designed to trap vapours will not necessarily remove aerosols. Aerosols cause special problems in sampling and analysis (see *Part 5.7, Supporting sciences, Sampling and analysis*) and techniques devised for diisocyanate vapour will not necessarily give satisfactory results with aerosols.

Large particles may be filtered out in the nasal passages or may not penetrate past the larynx when inhaled by the mouth. Smaller particles may penetrate further into the respiratory tract and at least some of the diisocyanate will probably react with the mucus which covers the surface of the bronchi. These reacted particles on the bronchi will be removed by mucociliary clearance. This is a mechanism by which materials are cleared from the lung. The conducting airways of the lung are lined with cells that have small surface projections called cilia, and other cells that secrete the protective mucus layer. The cilia move in a rhythmical way to direct the mucus film up the respiratory tract, preventing mucus build-up and also removing particles that may have penetrated into the lung. Ultimately the mucus is discharged at the top of the respiratory tract, and is swallowed.

It is important to note that diisocyanate aerosols generated by the spray nozzles used in workplace applications may have particle size distributions which are very different from those used in laboratory tests with animals. Accordingly, the extrapolation of the results of animal experiments to humans should be undertaken with caution. In Figure 3.2, curve A represents the distribution of highly respirable aerosol particles of polymeric MDI used in a study designed to assess the toxicity of polymeric MDI in rats under worst case conditions. Curves B and C, in contrast, represent the distributions of aerosol particles from two real-life situations. It will be noted that only a very small fraction of these particles are in the respirable range of humans.
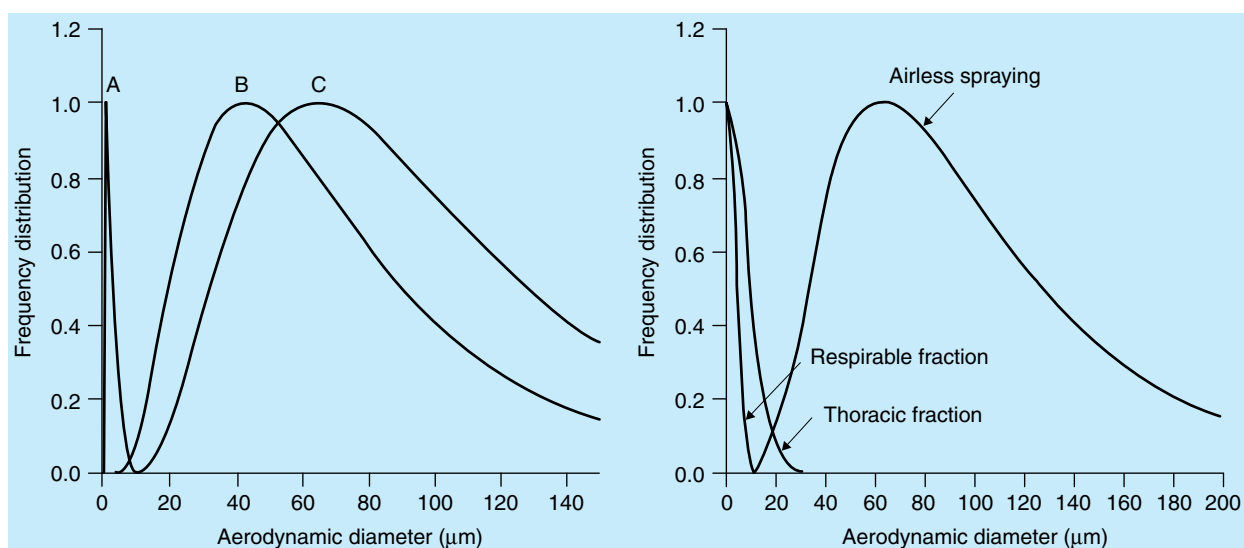
Figure 3.2 **Particle size distribution of aerosols: real life versus a laboratory toxicological study. (a) Comparisons of a toxicological study of polymeric MDI (curve A); manufacture of chipboard using polymeric MDI as the adhesive (curve B); airless coating of a surface using a fine nozzle (curve C). (b) Comparison of the particle size distributions in airless coating with fractions of medical relevance. Dr J Pauluhn (Bayer AG), personal communication**

Irritative effects to nose, throat and lungs

Exposure to TDI vapour or MDI aerosols grossly in excess of the occupational exposure limits can cause irritative effects to the respiratory system (nose, throat and bronchi).

Irritative effects of MDI or TDI are caused by exposure to concentrations considerably in excess of the maximum allowable exposure limits. In the case of TDI vapour the first symptom is usually a burning sensation in the eyes. As the concentration in the atmosphere increases, the characteristic smell is detected. Further exposure causes soreness in the throat, lachrymation of the eyes and nasal irritation. Continued high level exposure will cause coughing

and bronchitis. In extremely severe cases of over-exposure, accumulation of fluid in the lungs may occur (*pulmonary oedema*).

In one report (Henschler *et al*., 1962), three of six volunteer subjects noted eye irritation from a 65/35 mixture of 2,4- and 2,6-TDI at 50 ppb in the air within 10 min of exposure (cf. *Effects on the eyes,* above). After 15 min of exposure five of the six subjects reported such symptoms, with one also having nasal irritation. At 100 ppb there was strong irritation to the eyes and nose, with two subjects noting throat irritation. At 500 ppb TDI all six subjects had irritation of the eyes, nose and throat.

Symptoms shown by some foam workers
Alexandersson *et al*. (1985); Holness *et al*. (1984); Lee and Phoon (1992); Omae *et al*. (1992).

An excess of relatively mild symptoms has been reported in a number of studies of workers involved in the manufacture of TDI-based polyurethane foams. These symptoms include running nose, eye irritation, coughing and breathlessness. The workers exhibiting the symptoms were not identified as being sensitized to diisocyanates in any way. These symptoms may reasonably be attributed to irritative effects in the workplace, although they do not provide conclusive evidence that TDI was the sole cause of irritation of the eyes and respiratory tract. Whilst the workplace atmospheres would probably have contained low amounts of TDI vapour, they would often also have contained small amounts of other volatile foam-making chemicals such as solvents, blowing agents and tertiary aliphatic amine catalysts. In one case at least (Lee and Phoon, 1992) the exposure limits were regularly exceeded.

Reports of the irritative effects in man of MDI exposure are fewer than those of TDI, possibly because MDI was introduced commercially several years after TDI, and after it was realized that strict control of atmospheric concentrations of diisocyanates was necessary. Furthermore, MDI has a lower vapour pressure than TDI. Bystanders have been reported as suffering coughing, chest constriction and eye irritation during the spraying of rigid foam made with polymeric MDI (Longley, 1964) and similar symptoms have also been reported in other cases involving the manufacture of foams from polymeric MDI. It is not known what the true exposures to polymeric MDI were in any of these cases, and it should be noted that the aerosols inhaled would be of reacting mixtures and would contain several components other than polymeric MDI.

Asthma
General description
Asthma is a chronic inflammatory disorder of the respiratory tract, characterized by episodes involving narrowing of the airways, which are usually reversible (Figure 3.3), but can be severe and sometimes fatal. Asthmatic attacks are characterized by coughing, wheezing, tightness of the chest, laboured breathing, and by lung function disturbances due to narrowing of the airways caused by bronchoconstriction, excessive tenacious secretions of mucus, and swelling of the mucous membranes. Asthma can be a distressing and debilitating disease which can severely affect the patient's quality of life. Asthma is a very widespread disease in the general population and is found in up to 10 % of adults. Between asthmatic attacks, normal lung function characteristics may often be observed; later on, permanent airway obstruction may develop.

So far as the cause of asthma is concerned, a distinction is often made between extrinsic asthma and intrinsic asthma. Intrinsic asthma has no known
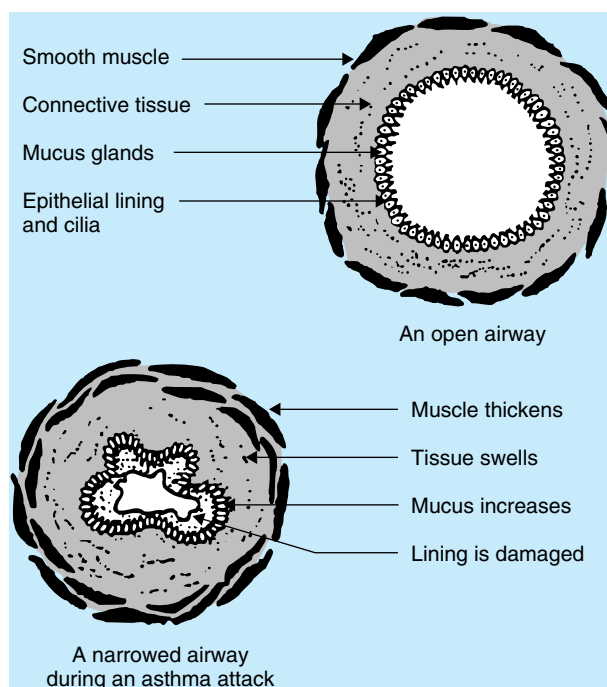
Figure 3.3 **The effects of asthma on the airways**

allergic cause. The mechanisms for this type of asthma are less well established. Extrinsic asthma, in contrast, is asthma caused by external agents, and individuals develop IgE antibodies to such agents. Individuals with extrinsic asthma are often described as being *sensitized* to the specific materials that precipitate their attacks.

Occupational asthma

Occupational asthma is asthma which is caused by specific agents, such as dusts, fumes, gases or vapours found in industrial environments. Occupational asthma due to high molecular weight agents is very similar to extrinsic asthma. It is not always possible to demonstrate IgE antibodies in asthma induced by low molecular weight agents. In contrast, aggravated asthma is pre-existing asthma that has been aggravated by irritants in the workplace. The occurrence of asthma of all types is increasing in many countries. Occupational asthma is not the main contributor to this increase, since the age group with the greatest increase is too young to be employed. However, a significant proportion of all asthma cases (2 to 15 % according to Becklake) are believed to be of occupational origin in many countries.

In the development of occupational asthma two distinct phases should be distinguished:

- The induction phase, during which specific mechanisms for bronchial hyper-responsiveness build up, due to over-exposure(s) to a specific agent.
- The reaction phase, in which asthma attacks are precipitated by small dose re-exposures to the specific agent.

References on occupational asthma
Becklake (1993); Johnson *et al*. (2000); Lagier *et al*. (1990); Liss *et al*. (2000); Maestrelli *et al*. (1997); McDonald *et al*. (2000); Morse (1994); van Kampen *et al*. (2000).

The onset of the asthmatic attack may be very soon after exposure, within minutes of re-exposure to the causative agents (immediate onset), it may be delayed for 4 to 8 h (delayed onset), or dual asthmatic reactions may occur (both immediate and delayed onset asthmatic attacks from the same re-exposure incident). Continuous or atypical asthmatic reactions may also occur. The late and the dual reactions may represent more advanced stages in diisocyanate asthma.

An extremely wide variety of causative agents of occupational asthma is known (Chan-Yeung and Lam, 1986). Amongst about 200 substances so far identified as causing asthma are many naturally occurring agents, including hardwood dusts such as Western red cedar, which is an important cause of occupational asthma in North America, castor bean dust, tea dust, dusts and flours from many grains, and animal-derived materials (crustaceans, fish and fish products, and the dander from laboratory animals such as rats and mice). In Finland, for example, the main causes of occupational asthma in 1992 were animal allergens (39.6 %), flours (24.8 %), other biological allergens (12.1 %) (Nordman, 1994). In Germany in 1993 to 1996 the main cause of occupational asthma was flour (Bolm-Audorff, 1997). MDI and TDI are amongst the many chemicals known to be capable of causing occupational asthma. Other examples include acid anhydrides, some antibiotics, sulphonamides, piperazine, biological enzymes, fumes from platinum, chromium and nickel salts, some reactive dyes and glutaraldehyde.

Diisocyanate asthma

Occupational asthma from MDI or TDI can occur where workplace exposures are inadequately controlled. In some countries asthma from diisocyanates can be a significant problem. Whilst it does not yet seem possible to weigh the importance of short-term peak exposures versus chronic exposure, experience suggests that the risk of asthma induction for normal, healthy persons is related to significant MDI or TDI exposures above 20 ppb.

Prevalence: the number of cases in a population at any one time.
Incidence: the occurrence of new cases per unit size of population within a given period of time.

The level of the prevalence and incidence depends on a number of factors, of which the most important seems to be exposure intensity (Diller, 1988), which is seldom reported. This has the effect of making it difficult to compare results between countries and between workplaces. Prevalences of diisocyanate asthma in small groups of workers where there has been insufficient control of occupational exposure have ranged up to about 25 %. In extreme cases, where wholly inadequate occupational exposure control situations existed, even higher prevalences have been found. In well-controlled work environments new cases of diisocyanate asthma would not be expected.

Cases of diisocyanate asthma, from both MDI and TDI, have been extensively reported, particularly in the earlier literature (NIOSH, 1978), at a time when no clear distinction was made between the clinical pictures of irritation and asthma and when exposure was higher than at the present day. Many of the reported case histories give only anecdotal information on the working conditions which gave rise to the asthma; the actual levels of exposure to diisocyanates were unknown in most cases.

Management action to isolate and ventilate adequately the processes where diisocyanate over-exposure can occur produces remarkable reductions in diisocyanate asthma (Wang *et al.*, 1988). A good example of how exposure influences the incidence of diisocyanate asthma has been given in a study of the development of asthma resulting from exposure to TDI in a TDI manufacturing plant over the period 1956 to 1974 (Porter *et al.*, 1975). During the 17 year history of the plant 30 of 300 workers in the population were judged to have developed occupational asthma from TDI. As the measured average airborne levels of TDI near the plant were reduced from about 60 to 20 ppb and lower, the new cases of TDI asthma decreased to zero.

References linking pulmonary problems with high diisocyanate exposure Bernstein *et al.* (1993); Bruckner *et al.* (1968); Moller *et al.* (1986a); Weill *et al.* (1981).

Several investigators have commented on the importance of peak exposures and spills of diisocyanates as causes of diisocyanate asthma. Brooks (1982) found more pulmonary problems, including asthma, in diisocyanate workers who reported that they had been exposed to more than 20 spills in the past. Other authors have reported similar findings. The relative prevalence of any specific occupational asthma in a country depends also on the economic structure. Thus, in the USA, Switzerland and the UK, diisocyanates have been reported to be the most significant causes of occupational asthma. Spray painting and spray insulation, coating and foaming are most often involved. The manufacture of diisocyanates and polyurethane elastomers and adhesives play a minor role. In predominantly agricultural economies, occupational asthma from natural products is more common than from the use of synthetic chemicals.

It is clear that many work processes involving MDI or TDI provide situations in which occupational asthma from diisocyanates can develop in the absence of appropriate workplace exposure controls. It is less obvious that diisocyanate asthma can also develop due to the thermal decomposition of polyurethanes with the liberation of diisocyanates and other species in small quantities. This may occur in the drilling, cutting or thermal welding of polyurethanes, and during the flame bonding of flexible polyurethane foams to textile substrates.

Examples of occupational asthma from MDI or TDI

TDI

Spray painting: Pisati *et al.* (1993)
Furniture painting: Paggiaro *et al.* (1984)
Steel coating: Venables *et al.* (1985)
Foam injection: Moller *et al.* (1986a)

MDI

Shoe sole manufacture: Mapp *et al.* (1985a)
Foundry moulding: Johnson *et al.* (1985)

Thermal decomposition of polyurethanes

Drilling: Dietemann-Molard *et al.* (1991)
Cutting: Chang and Karol (1984)
Flame bonding: HSE (1999)

Thermal decomposition of polyurethanes

The liberation of diisocyanates by thermal decomposition is caused by a partial reversal of the polyurethane-forming reaction. This dissociation occurs to only a very limited extent. A polyurethane coated wire, for example, released detectable concentrations of TDI at 220 °C and 370 °C, but not at 130 °C (Rosenberg, 1984).

There are no known cases of diisocyanate asthma developing from exposure to MDI- or TDI-based polyurethanes when used below temperatures which would cause thermal degradation, for example in the use of polyurethane foams for the insulation of hot water pipes.

The induction periods for the development of asthma from MDI or TDI are extremely variable. Occasional reports of asthmatic reactions on the first day of working with diisocyanates are most probably due to pre-existing non-specific bronchial hyperresponsiveness. Overall, the data suggest that 50 % of those who develop diisocyanate asthma do so within about 2 years of their first exposure, though in some populations up to 75 % of those who finally developed diisocyanate asthma had done so within 1 year. It is unclear to what extent this reflects the widely differing exposure levels to MDI or TDI that existed in the occupational settings studied and to what extent individual predisposition was involved.

See *Asthma onset* in *Further reading*.

Most populations with diisocyanate asthma include significant proportions of immediate onset, late onset and dual reactors. No strong relationships have been established to link age, gender, duration of workplace exposure, smoking or basal pulmonary function with the induction period for asthmatic responses.

Confounding factors in diisocyanate asthma induction

It is believed that there can be disparate influences on the development of occupational asthma (Figure 3.4) (Chan-Yeung and Malo, 1993). Several studies have been conducted to explore the potential involvement of possible
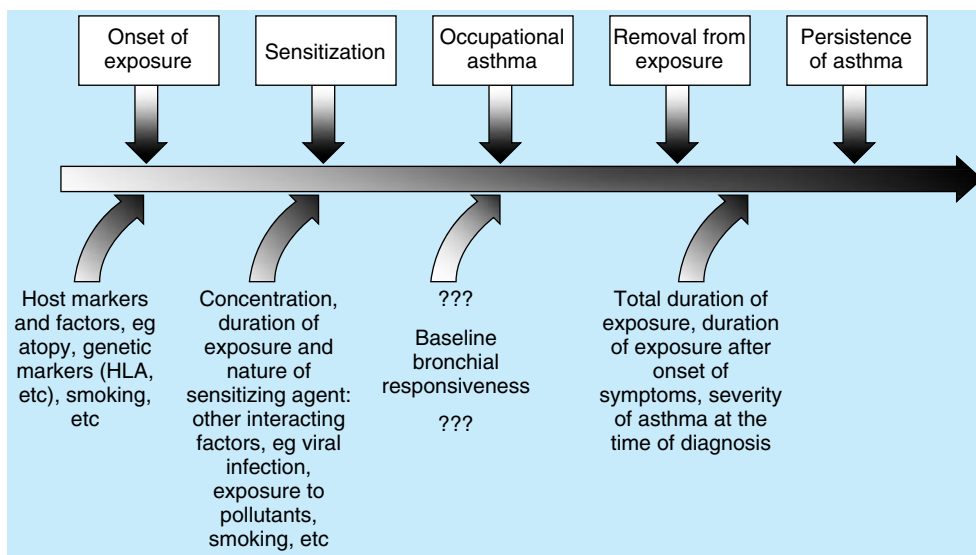
Figure 3.4 Development of occupational asthma. Figure redrawn with permission from *Asthma in the Workplace*, Marcel Dekker, 1993

causes (confounding factors) other than diisocyanates in the development of diisocyanate asthma. Amongst these factors are atopy and smoking, which are believed to be connected with either the development of asthma or with its severity.

It is not possible to identify predisposition to develop occupational asthma from MDI or TDI from the diagnosis of atopy.

Atopy

Atopy is defined as an inherited disposition for allergic diseases. Whilst the tendency to develop an allergy is inherited, the specific clinical form (hay fever, asthma, etc.) is not. Diagnostic indicators for this condition may be:

- personal or family history of allergic diseases;
- positive skin prick tests with common aero-allergens;
- an elevated level of total IgE antibodies in the blood serum.

The prevalence of atopy has been estimated as about one in four of the general population (Weeke and Poulsen, 1993). By definition, atopy predisposes an individual to allergic forms of asthma, including occupational asthma due to high molecular weight agents, such as flour and dander. Many researchers have therefore investigated the tendency of atopics to develop occupational asthma from MDI or TDI (low molecular weight agents). It was generally found that atopics were not grossly over-represented among diisocyanate asthmatics (Figure 3.5).
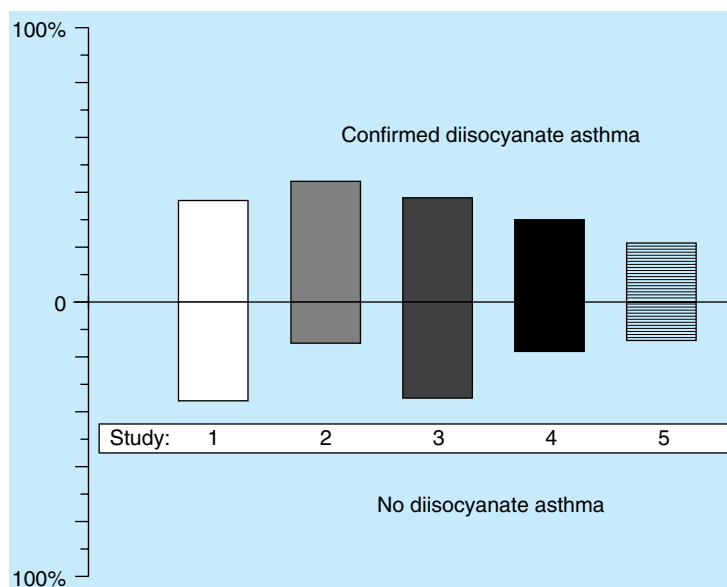
Figure 3.5 **Percentage of atopics in subjects with and without asthma from MDI or TDI (423 subjects). Study 1: Moscato *et al*. (1991), 63 subjects. Study 2: Paggiaro *et al*. (1984), 47 subjects. Study 3: O'Brien *et al*. (1979b), 63 subjects. Study 4: Banks *et al*. (1989), 63 subjects. Study 5: Mapp *et al*. (1988a), 162 subjects**

Smoking

Smokers do not seem to be more likely to develop diisocyanate asthma than nonsmokers.

It is well known that smoking has a number of deleterious effects on the lungs. In addition to causing the development of lung carcinomas following long-term inhalation of tobacco smoke, smoking also causes an increase in nonspecific bronchial hyperresponsiveness and an increase in the average rate of decline of some lung function parameters with age. Smoking, however, does not seem to be associated with any predisposition to occupational asthma from MDI or TDI: this can be seen from Figure 3.6 where the smoking habits of asthmatics in six diisocyanate-exposed populations are shown.
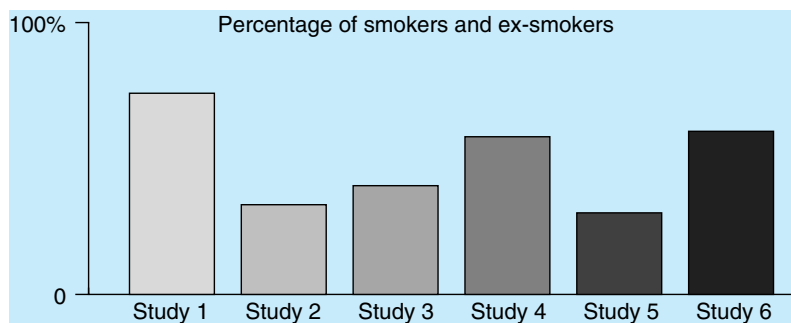
Figure 3.6 **Smoking habits of asthmatics. Study 1: Adams (1975), 42 subjects. Study 2: Mapp *et al*. (1988a), 93 subjects. Study 3: Moscato *et al*. (1991), 46 subjects. Study 4: O'Brien *et al*. (1979b), 37 subjects. Study 5: Paggiaro *et al*. (1984), 27 subjects. Study 6: Liss *et al*. (1988), 32 subjects**

Other confounding factors

Confounding factors seem to be of minor importance in the induction of diisocyanate asthma.

The involvement of other irritants in polyurethane workplaces (such as tertiary amine catalysts, solvents and wood dust), environmental pollution or viral infections cannot as yet be excluded as possible contributory causes.

Precipitation of attacks of diisocyanate asthma in sensitized subjects

Asthmatic attacks can be provoked in diisocyanate-sensitized subjects by concentrations of diisocyanates below the occupational exposure limits.

An asthmatic attack (with immediate, delayed, dual onset or continuous symptoms) may be provoked by exposures to concentrations of diisocyanates

well below the occupational exposure limits in subjects already sensitized. Therefore, working below the occupational exposure limits in well-controlled diisocyanate working atmospheres does not necessarily provide protection for sensitized persons against further attacks of asthma.

Typically, challenge concentrations up to 20 ppb for 15 min have been necessary to induce asthmatic attacks in many subjects (Banks *et al*., 1989; Lemière *et al*., 1996). However, for the most responsive sensitized individuals, challenge concentrations of down to 1 ppb of TDI have been found to provoke an asthmatic attack (O'Brien *et al*., 1979a; 1979b). Work with asthmatic subjects exposed to varied concentrations of TDI for different periods of time has shown that the main determinant of an asthmatic bronchial response to TDI is the total dose, and not concentration or duration of exposure (Vandenplas *et al*., 1993a).

Underlying mechanisms of asthma related to MDI or TDI

Diisocyanate asthma probably involves a spectrum of mechanisms, some immunological and some nonimmunological.

The mechanisms of diisocyanate asthma are still not fully understood in spite of extensive research work on both animals and man in academic and industrial centres. The capability of MDI and TDI to act both as irritant substances on airway surfaces at high exposure levels, and as multifunctional chemicals capable of reacting once or several times with biological constituents, leads to a wide spectrum of potential biomolecular outcomes. These include local irritative effects and the formation of diisocyanate reaction products with biomolecules. Diisocyanate asthma probably involves a spectrum of mechanisms, some immunological and some nonimmunological in origin.

Identification of the relevant immunological component(s) is still under debate. On the basis of animal models, one hypothesis to explain the development of diisocyanate asthma by immunological mechanisms can be described in a simplified way as follows.

The terms *conjugate* or *adduct* are often used to indicate a chemically bound biological reaction product with covalent links.

Upon the inhalation of diisocyanate vapour or aerosol, chemical reactions may take place with macromolecular or cellular components of the airway surface, for example with human serum albumin (HSA). The resulting compounds, adducts (conjugates), will be presented by special cells to the immune system and some of these new compounds will be recognized as foreign to the system. The immune system thereupon produces a specific defence by the production of lymphocytes and antibodies against these new compounds. These lymphocytes and the antibodies, both of which are bound on the surface of specific cells (mast cells), are stored in various body compartments. This process, which may take a few weeks, is called the induction period. Some of these specific antibodies can be found in the blood or skin and can be detected by methods such as RAST, ELISA and skin prick tests.

RAST: radioallergosorbent test. ELISA: enzyme-linked immunosorbent assay.

Upon re-exposure, a complex sequence of immunological mechanisms can take place (Figure 3.7), which results in the release of biologically active substances, such as histamine. These substances, together with sensitized lymphocytes, can cause either immediate or delayed asthmatic attacks.

Induction phase	Reaction phase
Inhalation of diisocyanates	Re-exposure to diisocyanates
↓	↓
Formation of "conjugates" in the respiratory tract	Antigen - antibody - reaction on mast cell surfaces of respiratory tract
↓	↓
Immune system produces specific antibodies and lymphocytes against "foreign" conjugates	Release of various mediators from mast cells (histamine etc.)
↓	↓
Specific antibodies and lymphocytes circulate in blood stream and antibodies may also be held on the surface of tissue mast cells	Mediators provoke various types of acute asthmatic reactions within bronchial tissues, as well as a state of non-specific bronchial hyperresponsiveness

[W F Diller, International Conference on Occupational Health, Stockholm 1996]

Figure 3.7   **Some mechanisms in diisocyanate asthma**

RAST and ELISA involve the use of synthetic human serum albumin reaction products (or conjugates), and researchers have used a number of methods to react MDI or TDI with HSA *in vitro*. Because of the possibility that several different reactive groups on the HSA could be involved, and since either one or both of the isocyanate groups in MDI or TDI can potentially react, it is likely that different preparative methods of the conjugate will result in different end products. The reproducible preparation of diisocyanate−HSA reaction products poses considerable experimental problems which may lead to a large variability and inconsistency of results. The conjugate prepared for the RAST test under laboratory conditions may therefore not be identical to that formed under conditions existing in the human respiratory tract.

Antibodies IgE and IgG

Immunoglobulin (Ig)E is the most important antibody involved in immediate allergic responses. It is normally present in blood serum at very low levels (approximately 2×10^{-5} mg/ml).

Immunoglobulin (Ig)G is important in combatting foreign cells, toxins, bacteria and viruses. It is present in blood serum at approximately 12 mg/ml (15 % of total human adult blood serum protein).

Many investigators have attempted to measure IgE and IgG antibodies specific to MDI or to TDI in the sera of diisocyanate-asthmatic subjects. Specific diisocyanate antibodies have been found in the serum of less than 20 % of diisocyanate asthmatic subjects (Baur *et al*., 1994). False positive results have been observed with specific IgE antibodies, while elevated IgG antibody levels have been found to correlate with diisocyanate exposure rather than with occupational asthma.

Another problem in the identification and measurement of antibodies specific to diisocyanates is the observation of cross-reactivity of specific antibodies. In these cases, the antibodies in the serum of a worker exposed to one particular diisocyanate were found to recognize the HSA conjugate prepared from a second diisocyanate. This lack of antibody specificity has also been found in studies in which test animals have been exposed to only one diisocyanate. Further information can be found in reviews by Fabbri, Baur, and their co-workers (Fabbri *et al*., 1994; Baur *et al*., 1994).

Cross-reactivity of specific antibodies
Baur *et al*. (1994); Baur (1983); Grammer *et al*. (1990); Tse *et al*. (1985).

Diagnostic procedures

The degree of certainty of a diagnosis (validity) will depend on the requirements of each individual case. A stepwise approach can be used, leading to an increasing level of confidence in the diagnosis. However, in some cases, particularly when the onset of asthma occurred some time previously, unequivocal diagnosis of diisocyanate asthma can be difficult, and the physician may form an opinion based on the balance of probabilities.

In the following, a summary of the currently used diagnostic procedures is presented as they are described in the relevant literature. Development of new methods, scientific advancements and the growing experience of the experts will change the various approaches continuously. The information given below can, therefore, reflect only the current status. *Appendix 1* to this Part gives more detailed information on the steps that a physician may wish to follow to provide a diagnosis. The diagnostic steps summarized below are based on scientific publications and authoritative guidelines for occupational asthma, which should be consulted for additional details (Maestrelli *et al*., 1992; ECETOC, 1993). A stepwise procedure is generally recommended, though there are various modifications. The steps are:

- Step 1: confirmation of work-related asthma;
- Step 2: confirmation of the causal role of diisocyanates;
- Step 3: exposure testing.

STEP 1 Confirmation of work-related asthma
Step 1 usually comprises relatively simple procedures which will substantiate the suspicion of occupational asthma and will suffice for decisions on workplace relocation for an individual.

Confirmation of bronchial asthma:

- personal history (see *Appendix 2* to this Part).
- lung function testing. This is frequently carried out by spirometry, which measures FEV_1 and other parameters and which requires the active cooperation of the patient. In some countries, whole-body plethysmography is preferred. This technique measures, among other parameters, the airway resistance by means which are not dependent on the cooperation of the patient.
- bronchodilation test.

- test for nonspecific bronchial hyperresponsiveness (NSBH) (see *Appendix 1* to this Part).

Since asthma is characterized by variable airflow obstruction, the essential symptoms may be absent at the time of examination by a physician. If, however, bronchoconstriction is present then a significant improvement in FEV_1 can be observed after inhalation of an aerosol of a bronchodilator administered by a physician.

Confirmation of the work-relationship of the asthma:

- occupational history;
- across-shift lung function;
- serial measurement of peak expiratory flow.

The physician will wish to establish that there is a causal relationship between exposure to MDI or TDI in the workplace and the occurrence of the air flow obstruction. Symptoms may develop whilst the subject is at home, even during the night (delayed or late-onset asthma). There is often a significant interval between the first diisocyanate exposure and the development of asthmatic symptoms. Symptoms may improve during absences from work, for example at weekends.

Serial measurements of peak-expiratory flow can be a very valuable diagnostic tool and can be measured with a simple portable meter (Figure 3.8). Useful results require the active cooperation of the patient to provide accurate flow readings. The results must always be carefully interpreted by a physician.

Peak expiratory flow, the peak rate at which air can be exhaled using maximum effort is often measured with a portable meter which the subject can use at intervals during the working day and at home.

Work-related episodic bronchoconstriction is a critical part of the diagnosis of diisocyanate asthma. It may be confirmed by the frequent self-measurement of the peak flow rate during the time spent awake. Measurements every 2 to 4 h are recommended to obtain sufficient data for interpretation.

Figure 3.8 **Peak flow meter. Reproduced by permission of Clement Clarke International Ltd**

For legal purposes, such as for compensation claims, a higher degree of probability and specificity is necessary. This can be achieved by additional steps which require more sophisticated methods.

STEP 2 Confirmation of the causal role of diisocyanates
Positive immunology such as RAST, ELISA, skin prick tests.

Only a small proportion of proven diisocyanate asthmatics exhibit a positive radioallergosorbent test (RAST). Absence of recent diisocyanate exposure can also be a reason for false negative results. False positive test results also can arise if there is a high level of total nonspecific antibody in the blood sera, or because of faulty interpretation of background levels of antibodies in normal subjects.

STEP 3 Exposure testing

- A workplace exposure test (see *Appendix 1*).
  or
- a specific inhalation challenge test.

A specific inhalation challenge test involves exposure of the patient to known concentrations of the diisocyanate vapour or aerosol under strictly controlled laboratory conditions. These tests are considered the most definitive tests, but they are not available in all countries. Challenge tests can also give false positive results (for example, due to cross-reactivity problems, to the use of excessively high concentrations of test substances or due to subjects having extreme nonspecific bronchial hyperresponsiveness) or false negative results (for example, due to testing a long time period after workplace exposure to diisocyanate). These tests should be carried out in specialized laboratories, only under the close supervision of an experienced physician. Normal healthy subjects generally do not react positively on specific inhalation challenge testing over a period of 30 min at concentrations below the short-term occupational exposure limit of MDI (20 ppb, which is $0.2\,\mathrm{mg/m^3}$) or TDI (20 ppb, which is $0.14\,\mathrm{mg/m^3}$) (Cartier *et al*., 1989).

Outcome of asthma from MDI and TDI

Early diagnosis of diisocyanate-induced asthma and complete removal of the patient from further exposure are very important indeed if the long-term effects are to be avoided.

Occupational asthma in general has a variable prognosis, and overall just about 50 % of subjects fully recover after cessation of exposure. Diisocyanate-induced asthma is no exception. However, the data derived from many published studies may be biased because they are based on patients with more severe asthma or with more persistent symptoms than those seen by plant physicians and local practitioners, and may therefore not be representative of all patients who develop diisocyanate-induced asthma. Those who have the least exposure to TDI, or for the shortest time, or those with the least severe symptoms or who are in a younger age group tend to recover more fully.

It may be many years after cessation of exposure of the subject before all the symptoms disappear. In the more severe cases, permanent impairment of lung performance may result, with the possible development of chronic obstructive lung disease with or without a much heightened asthmatic response to a wide range of nonindustrial agents, including dust, car exhaust fumes, and cold air (nonspecific bronchial hyperresponsiveness). See Table 3.3.

Table 3.3 **Outcome of asthma from diisocyanates.**

Number of subjects	Follow-up period	Recovered %	Improved %	Not improved %	Reference
Subjects who left exposure					
114	1.8 years (average)	20	53	27	Tarlo *et al*. (1997)
43	5 years	28	23	49	Pisati *et al*. (1993)
35	2 years	49	31	20	Park and Nahm (1997)
30	11 months (average)	23	3	73	Mapp *et al*. (1988b)
20	3 to 8 years	55	5	40	Adams (1975)
9	18 to 73 months	44	0	56	Paggiaro *et al*. (1993)
Subjects who continued exposure					
17	5 years	0	0	100	Pisati *et al*. (1993)
15	Up to 2 years	7	0	93	Paggiaro *et al*. (1984)
10	About 2 years	0	30	70	Tarlo *et al*. (1997)
5	11 months (average)	0	0	100	Mapp *et al*. (1988b)

In six subjects with less severe delayed-onset asthmatic reactions to TDI, the nonspecific bronchial hyperresponsiveness had returned to normal within 1 month (Mapp *et al*., 1985b). In other cases this hyperresponsiveness may last for a long period of time, in some cases for many years. In one extreme case, a worker drenched with TDI in an accident had retained his TDI hypersensitivity and a high level of nonspecific hyperresponsiveness 12 years after immediate removal from further TDI exposure (Moller *et al*., 1986b).

Once diisocyanate-induced asthma has developed, further exposure to even low amounts of diisocyanate often leads to respiratory deterioration with severe symptoms and impaired lung function performance.

Nonspecific bronchial hyperresponsiveness

Nonspecific bronchial hyperresponsiveness is often, but not always, present in subjects with asthma from MDI or TDI.

Some individuals show exaggerated responses to a wide variety of weak bronchoconstrictive stimuli such as cold air, heavy exercise, and various airborne allergens and irritants such as kitchen fumes and cigarette smoke. In these individuals, exposure to appropriate stimuli may cause various degrees of chest

constriction, cough, shortness of breath, laboured breathing, wheezing and asthma-like attacks. This condition is often referred to as nonspecific bronchial (or airway) hyperresponsiveness (NSBH).

Measuring nonspecific bronchial hyperresponsiveness (NSBH)

NSBH can be diagnosed and quantified by inhalation tests with aerosols of agents which cause bronchoconstriction such as histamine, methacholine, cold air or hypertonic saline. The tests must be carried out by an experienced physician in a laboratory with adequate support facilities. NSBH is often expressed as the concentration or the cumulative dose of agent producing a 15 % or a 20 % fall in FEV_1. See *Appendix 1* for further information.

The reasons why some people have NSBH are not fully understood, though genetic predisposition, recent viral infections such as influenza, as well as environmental factors may be involved. Several excellent overviews on measuring or interpreting nonspecific bronchial hyperresponsiveness are available and should be consulted for further details (Chan-Yeung, 1993; Hargreave *et al.*, 1986; Sterk *et al.*, 1993).

The presence of NSBH may provide an explanation for the asthmatic symptoms shown by a few individuals on exposure to MDI or TDI during their first days at their workplace, even when levels of diisocyanate vapours are below the occupational exposure limits and when other workers are completely unaffected.

While NSBH is usually associated with asthma, including asthma caused by MDI or TDI, its degree may be variable. Studies in which the presence of NSBH has been investigated in subjects diagnosed as having asthma from MDI or TDI have given inconsistent results. In most of the studies, the majority of the asthmatic subjects also had NSBH, but there were often significant numbers of asthmatics without NSBH (see *NSBH in asthmatics* in *Further reading*). The observed differences in the prevalence of NSBH in such patients may be due to the different methods used to determine the NSBH and to differing levels of the severity and persistence of the underlying diisocyanate asthma.

Excess lung function decrement

For both MDI and TDI, the available studies suggest that excess lung function declines do not occur if the exposure is maintained below the current time-weighted average occupational exposure limit of 5 ppb.

Human lung function is known to decline gradually with increasing age in every individual. The lung function parameters most used in the clinical situation are the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC). These parameters are also most commonly used to quantify possible excessive changes in lung function with time in epidemiological studies.

Epidemiology: the study of effects in populations.

Various influences may cause a decline in lung function greater than that expected with normal ageing. Smoking is the most commonly encountered and best researched of these. Inhalation of irritating substances, such as air pollutants, is an additional factor that could effect a change in lung function. Since diisocyanates are known to act as irritants at high concentrations, numerous

studies have been undertaken to investigate whether diisocyanates contribute to excess lung function declines at workplace exposure concentrations.

There is still considerable variation in lung function parameters between individuals even after allowing for all known influences. Therefore, epidemiological studies with large cohorts may be required to assess subtle but meaningful shifts in lung function.

Important criteria for assessing studies of lung function decrement in diisocyanate-exposed populations

- A large study population is desirable, to account for normal variability between subjects, and to distinguish small effects.
- The effects of recognized lung decrement risk factors, such as cigarette smoking, should be addressed.
- Known asthmatics should be treated separately in the analyses, as their results may mask other pulmonary effects.
- There should be few leavers from longitudinal studies.
- An internal control population should be available with which to compare results.
- Diisocyanate concentrations should be measured in the breathing zones of workers.
- Diisocyanate peak and average concentrations both need to be examined.
- A meaningful number of representative air samples should be analysed for diisocyanates.

Epidemiological studies on diisocyanates are difficult and expensive to undertake if they are to produce robust findings, since several important criteria need to be addressed. The main epidemiological approaches are cross-sectional and longitudinal studies on suitable exposed populations:

- Cross-sectional studies are those in which a population is examined so far as is possible on one occasion, or over a very limited time period. Exposure and job history data are obtained, enabling an assessment of the intensity and duration of exposure. The lung performance charac teristics of each individual are measured including those of a sufficiently large unexposed control group. Statistical analyses are then carried out to examine if there are any meaningful associations between lung performance and diisocyanate exposure after allowing for age, smoking habits, gender differences and any known confounding parameters (for example, health problems unconnected with the study, exposures to other chemicals, prior job histories, etc.).

- Longitudinal studies are those in which the study population is identified and is followed for a number of years. The lung performance of each individual (as well as those in a control population) is measured at intervals over a study period. As with cross-sectional studies, statistically significant relationships are then sought between exposure patterns and lung performance. With longitudinal data, the outcome variable is often expressed as an annual rate of decline in lung function.

Although many epidemiological studies have been carried out on possible lung decrements due to diisocyanate exposure, there are no studies existing which meet all the characteristics for an ideal epidemiological investigation. Obviously, interpreting the validity of studies and combining results across studies requires great care. Garabrant and Levine (2000) completed an independent review of all the then available MDI and TDI population studies with well-documented exposure data. The populations totalled in excess of 2400 workers and covered subjects from both TDI manufacturing and polyurethane foam plants in many different locations. The diisocyanate exposure scenarios differed significantly, with the earlier studies generally reporting the higher ambient diisocyanate exposure levels. The earlier studies relied upon area monitoring

See *Excess lung function decrement* in *Further reading*.

of exposure, no personal monitoring system then being available, and it seems likely that they may have underestimated the average diisocyanate exposure levels of the workers. A critical review of the exposure assessment techniques used in these studies is given in *Part 5.7, Sampling and analysis.* In some of the earlier studies diisocyanate asthmatics had been included in the summary statistics, resulting in distortion of the findings. Table 3.4 summarizes five of the larger and most recent studies; each was supported by extensive monitoring of the TDI exposure levels.

Table 3.4 **Larger longitudinal epidemiological studies on TDI-exposed populations.**

Type of work	Population size	Years studied	Study conclusions	Reference
TDI manufacturing	223	5	An excess FEV_1 decline was found for those spending time above 20 ppb TDI. Authors support the OEL of 5 ppb TDI for 8 h time-weighted average.	Diem *et al*. (1982) Weill *et al*. (1981)
TDI manufacturing	313	at least 5	There was no relation between cumulative exposure to TDI and decline in FEV_1. TDI exposure levels were from 0.5 to 9.9 ppb.	Ott *et al*. (2000)
TDI manufacturing	305	26	FEV_1 declines were not related to observed TDI exposures (mean values 2.3 ppb TDI)	Bodner *et al*. (2001)
Polyurethane foam manufacturing	227	5	FEV_1 declines were not related to observed TDI exposures (mean values 1.2 to 4.5 ppb TDI)	Jones *et al*. (1992)
Polyurethane foam manufacturing	521	5	FEV_1 declines were not related to observed TDI exposures (mean value 1.2 ppb TDI)	Clark *et al*. (1998)

The review of the data by Garabrant and Levine already cited strongly supported the conclusion that there was no long-term effect on FEV_1 from exposures to TDI that were below 5 ppb time-weighted average for subjects who were not sensitized.

There have been a few satisfactory studies with well-characterized exposure scenarios exploring the effects of MDI exposures alone on annual changes in FEV_1. From the analysis of the published studies, it is similarly reasonable to conclude that occupational exposures to MDI below 0.05 mg/m^3 (approximately 5 ppb) time-weighted average are without risk of adverse acute or chronic effects on the respiratory system in nonsensitized subjects.

Alveolitis (hypersensitivity pneumonitis)
General description
Alveolitis, or hypersensitivity pneumonitis, affects the alveolar level of the respiratory tract, that is, the terminal sacs or air pockets in the depths of the lungs. Alveolitis may be induced by the repeated inhalation of a wide variety of materials usually in particulate forms as dusts or aerosols. The offending agents may be bacteria, fungi, proteins or chemicals. A commonly reported form of alveolitis is farmers' lung and is associated with the handling of mouldy hay. Re-exposure of persons with this condition to the offending agent (even below the occupational exposure limits, as applicable) may give rise to symptoms similar to those of influenza. These symptoms may appear some 6 to 8 h after

Pneumonitis: inflammation of the lung tissue.

re-exposure and may include malaise, joint pain, fever, cough, and shortness of breath. A chest X-ray might reveal an image similar to that associated with viral pneumonia with which this condition can be confused. Alveolitis should be suspected when an individual repeatedly develops influenza-like symptoms after a work shift. Immunological testing for IgG can be helpful in making the diagnosis. The signs and symptoms of an attack of alveolitis usually disappear within hours or a few days after cessation of exposure. However, if exposure is continued, chronic lung fibrosis, with impaired gas exchange, laboured breathing and reduced physical fitness, may develop.

Examples of alveolitis from MDI or TDI

MDI

Foam manufacture, adhesive use, foundry work	Baur (1995)
Wood chip board manufacture	Vandenplas *et al*. (1993b)
Foundry work	Schwarz *et al*. (1989)
In situ foam packing	Baur *et al*. (1984)
Shoe-sole manufacture	Mapp *et al*. (1985a)

TDI

Foam manufacture, spillage	Charles *et al*. (1976)
Bath tub paint spraying	Fink and Schleuter (1978)
Automobile paint spraying	Yoshizawa *et al*. (1989)

Alveolitis from MDI and TDI

Alveolitis from diisocyanates is a rare form of diisocyanate hypersensitivity. There are more cases of diisocyanate-alveolitis from MDI than from TDI. The reasons for the preponderance of MDI cases are unknown, but may possibly be due to the different forms of exposure in workplaces, with TDI as vapour and MDI sometimes as aerosol. Cross-reactivity between diisocyanates has been noted (Beysens *et al*., 1985). Alveolitis may occur in combination with asthma (Mapp *et al*., 1985a).

Reactive airways dysfunction syndrome (RADS)

If an excessively high concentration of an irritant gas or fume is inhaled on a single occasion, asthma-like adverse effects can ensue (Brooks *et al*., 1985). The immediate irritation can be followed by a condition like NSBH (see above). This adverse effect has been termed reactive airways dysfunction syndrome (RADS). RADS is characterized by persisting cough, shortness of breath, chest constriction and wheezing.

The causes, such as a major spillage or clothes saturated with the irritant agent, can usually be readily identified. A variety of causative agents have been reported, including anti-freeze (propylene glycol), uranium hexafluoride, hydrocarbons, spray paint, hydrazine, diisocyanates and fumes from welding.

Since RADS was not defined or characterized before 1985 it is possible that cases with single diisocyanate over-exposure prior to 1985 would now also be diagnosed as RADS. For

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Indicators for the diagnosis of RADS

- absence of preceding respiratory complaints;
- onset of symptoms after a single over-exposure;
- exposure to an irritant gas, smoke or fume present at a very high concentration;
- onset of symptoms within 24 h after exposure, with persistence for at least 3 months;
- symptoms similar to those of asthma (cough, wheezing and shortness of breath predominating);
- positive tests for nonspecific bronchial hyperresponsiveness;
- pulmonary function tests show airflow obstruction;
- other types of pulmonary disease excluded;
- no immunological involvement.   Brooks *et al*. (1985)

example, RADS-like symptoms were observed in firemen involved in fighting a fire in a factory making polyurethane foams from TDI, when a massive TDI spillage resulted after two large TDI storage tanks were damaged (Axford *et al*., 1976). Respiratory symptoms persisted in 20 men for several years. However, in this accident the firemen were exposed to a wide variety of chemicals.

RADS has been described after two police officers were exposed to high concentrations of TDI following a tank car accident (Luo *et al*., 1990). One subject developed symptoms about 4.5 h after initial exposure, the other immediately on exposure. In these cases the adverse respiratory effects persisted for several years with continuing airway hyperresponsiveness, which required treatment.

Other health effects of MDI and TDI

Effects on organs other than the lung have occasionally been attributed to MDI or TDI, but mostly without convincing evidence. Many of the effects have only been observed with one individual and there are no records available of the levels to which the subjects were exposed.

See *Other reported health effects of MDI or TDI* in *Further reading*.

Several haematological changes associated with MDI or TDI exposure have been reported, as have cardiovascular diseases and disorders of the central nervous system.

A few case studies have been reported of situations where extremely high exposure to either MDI or TDI has occurred by both the inhalation and dermal routes. In addition to respiratory symptoms, other complaints have also subsequently been reported. These have included headache, difficulty in concentrating, irritability, poor memory and confusion that improved months after, but did not completely resolve during follow up. It is not possible to be sure that the effects were due to diisocyanate exposure, as other chemicals were present.

A condition has recently been described as multiple chemical sensitivity (MCS) based on a broad and inconsistent variety of symptoms originating from different organ systems including headache, sleep dysfunction, loss of concentration, fatigue, anxiety, shortness of breath, dyspepsia and dysmenorrhoea. Clinical signs are lacking. The diagnosis is based entirely on subjective symptoms. Most probably, the term MCS covers a range of different disorders. Some patients may suffer from true occupational disease including diisocyanate asthma, while the majority meet the criteria of psychiatric conditions. See *Further reading: Multiple chemical sensitivities*. Though mainstream medicine has not accepted MCS as a defined disease, a number of countries today recognize MCS as a condition for which compensation may be awarded.

Cancer incidence studies
Hagmar *et al*. (1993);
Schnorr *et al*. (1996);
Sorahan and Pope (1993).

There have been three studies of the mortality and cancer incidence in worker populations employed in polyurethane foam factories using TDI. In total, the studies covered over 17 000 workers in Sweden, the USA and the UK. Some of the subjects had worked in the factories for many years, and during periods when workplace exposures were less well controlled than they are currently. None of the populations surveyed had death or overall cancer rates in excess

of those expected from normal populations. The levels of mortality in the populations were quite low (less than 10 %) at the times of the studies. The findings, though encouraging, are therefore not yet conclusive.

The toxicological work discussed later in this text on TDI administered to laboratory animals by inhalation (Loeser, 1983; Reuzel *et al*., 1994a) and on the inhalation of MDI aerosol strongly suggests that neither MDI nor TDI would be carcinogens in the workplace, even though they cause adverse irritative effects to the nasal and lung passages. A quantitative risk assessment has been made of the carcinogenicity of TDI to humans, possibly as a result of inter- mediate formation of TDA in the body by hydrolysis of TDI during inhalation exposure (Doe and Hoffmann, 1995). The data were taken from measurements of the toxicokinetics of TDI in rats at the occupational exposure limit. The risk assessment showed that TDI exposure by inhalation at the recommended occupational limit would not give rise to significant human carcinogenic risk. It seems safe to conclude that the carcinogenic risk from exposure to MDI or TDI in workplace situations is, at the very worst, extremely low.

The animal work on MDI and TDI described below strongly suggests that there should be no significant adverse health effects related to prenatal or reproductive toxicity.

Biomonitoring of MDI and TDI

Despite the recent developments reported in the published work on the biomonitoring of diisocyanates, much more information is required on interpersonal variability of diisocyanate metabolism and on the rela- tionships between aerosol concentrations and the rate of production of metabolites before there can be routine diagnostic use of these tech- niques. Caution must also be applied if diisocyanate prepolymers or reacting mixtures are believed to have been inhaled, as the metabolism of these substances may be different from that of MDI or TDI alone. The detection of MDA or TDA after acid treatment of biomonitoring samples should not be taken as evidence for the occurrence of the free aromatic amines (MDA or TDA) in the body.

Biological monitoring of humans who are potentially exposed to MDI and TDI in their workplace activities has received increasing attention in recent years. The work involved in measuring metabolites of MDI and TDI is of particular interest. It offers the potential of identifying high exposure tasks or work practices, as well as longer-term relationships between exposure and biological effects. It also provides a measure of the total dose of diisocyanate absorbed into the body by whatever route (lung, skin or mouth). Biomonitoring of MDI and TDI depends on an adequate knowledge of their kinetics and metabolism following inhalation, and possibly also after skin contact. Both urine and blood plasma samples offer sources of relevant metabolites. Of these, regular urine sampling is much less invasive for those involved.

Urine metabolites from TDI are found mainly as acid-labile reaction products from which TDA can be recovered after acid hydrolysis. The biological half-

Biological monitoring of TDI
Brorson *et al*. (1991); Maître
et al. (1993); Skarping
et al. (1991).

*Identification of MDA from
hydrolyzed urine or blood
plasma*
Boeniger *et al*. (1991);
Brunmark *et al*. (1995);
Schütze *et al*. (1995);
Skarping *et al*. (1994, 1995);
Skarping and Dalene (1995).

BAT: Biologische
Arbeitsstofftoleranzwert
(biological working
tolerance level).

lives of the TDI urinary metabolites from human volunteers exposed to known concentrations of TDI below the occupational exposure limit have been shown to be approximately 2 to 5 h. The cumulative amount of urinary metabolites eliminated over 1 day was related to the initial TDI inhalation exposure levels. Biomonitoring of total TDI exposure is therefore possible with highly sensitive analytical methods.

Blood plasma protein adducts of TDI were also related to TDI concentrations in the air with plasma metabolites being more slowly eliminated: a half-life of over 6 days was found after an initial rapid elimination phase. The occupational exposure of some TDI exposed workers involved in polyurethane manufacture has been studied by the biomonitoring of urinary and plasma metabolites (Rosenberg and Savolainen, 1986; Persson *et al*., 1993).

It has also been possible to quantify MDA after hydrolysis of urinary metabolites from MDI-exposed workers and from a worker who heated (350 to 600 °C) MDI-based polyurethane conveyor belts during manufacture and repair. The signs and symptoms shown by the latter worker suggested alveolitis and rhinoconjuctivitis. In Germany a urinary BAT level for MDI was recommended in 1997 (10 µg MDA/g creatinine).

Experimental toxicology

The toxicology of MDI and TDI has been well investigated in experimental animals and biological systems. The diisocyanates are relatively nontoxic by the oral route. When inhaled as aerosol or vapour, MDI and TDI cause effects, particularly on the respiratory tract, to which they are irritants. Both MDI and TDI are also irritating to skin and eyes. In animals, both MDI and TDI have given positive results in standard skin sensitization tests. There has been extensive investigation of the capability of MDI and TDI to cause respiratory sensitization in animals; however, there is currently no animal system that satisfactorily models the effects seen in humans.

Diisocyanates react very rapidly in the lung and are not available systemically as isocyanate. Absorbed material circulates in conjugated forms.

Repeated inhalation exposure studies have assessed effects on reproduction and on the developing foetus. No significant effects on reproduction have been found. Inhalation studies have also been used to investigate the carcinogenic potential of MDI and TDI. No carcinogenic effect was found in a study of a lifetime inhalation of TDI vapour. An increase in the incidence of lung adenomas in a similar study with polymeric MDI aerosol was probably associated with the prolonged irritation and inflammation seen. Some repeated dose toxicity studies have been done with orally administered TDI; however, this is a most unlikely route of exposure, and results are of very limited use to human risk assessment.

The basis of experimental toxicology

There is a wide range of biological processes which can be affected adversely by chemicals, both natural and synthetic. In order to understand what effects a chemical may have, a philosophy of assessing individual chemicals has evolved over the last three decades and the methods have been the subject of international agreement. A series of study designs has been developed which starts off with the aim of answering a general open question: *What effects has this chemical the potential to cause?*

The approach to answering this question starts with laboratory animals being exposed to the chemical for increasing periods of time and to increasing concentrations. This is in association with a wide range of examinations made on the health status of the animals. These include microscopic examination of all the major organs and systems. Study designs have been agreed by groups of experts throughout the world serving such organizations as the OECD, USEPA and the European Union, and their validity is accepted in all of the major countries and regions of the world. In addition, these studies generally are carried out under a set of strict quality assurance regulations called Good Laboratory Practice (GLP). All laboratories that wish their data to be considered by regulatory authorities must comply with GLP.

The philosophy behind these studies is to try to assess the risk of adverse health effects which can be expected from different exposures to a chemical. In order to make the assessment more rigorous, the doses used in these studies are often very high compared with expected human exposure in the workplace or in the community. If a chemical is found not to cause effects in animals at these high doses there is a high level of confidence that the chemical will not cause such effects in humans at similar or lower doses. In a way, the dice are loaded against the chemical and it is not surprising that many effects are seen which will be relevant only to high exposure or particular routes of exposure. If a particular effect is found in these studies then further specific studies are carried out to develop an understanding of the factors affecting toxicity. Importantly, specific observations are often made to determine whether there is any evidence that the effects seen in laboratory animals are seen in humans in typical workplace situations.

These studies are, in essence, dealing with the effect of a substance on the set of chemical processes which represent mammalian biochemistry. A discussion of the biochemistry of the diisocyanates must start with how they enter the body, and the biological systems with which they interact.

The interaction of MDI and TDI with biological systems

Absorption, distribution, metabolism and excretion

Studies have been carried out on the absorption, distribution, metabolism and excretion of diisocyanates. None of these processes involve free diisocyanate. In nearly all cases absorbed material circulates around the body as reaction products with biomolecules prior to metabolism and excretion.

The predominant chemical and biochemical reactions of MDI and TDI in biological systems are shown in Figures 3.9 and 3.10. Hydroxyl groups, amino groups, and sulphydryl groups are all found in biological systems. MDI and TDI have the potential to react with these groups and with water, by whatever route the diisocyanates enter the body (Brown, 1987), and therefore it can be assumed that no unreacted diisocyanate circulates around the body after absorption.
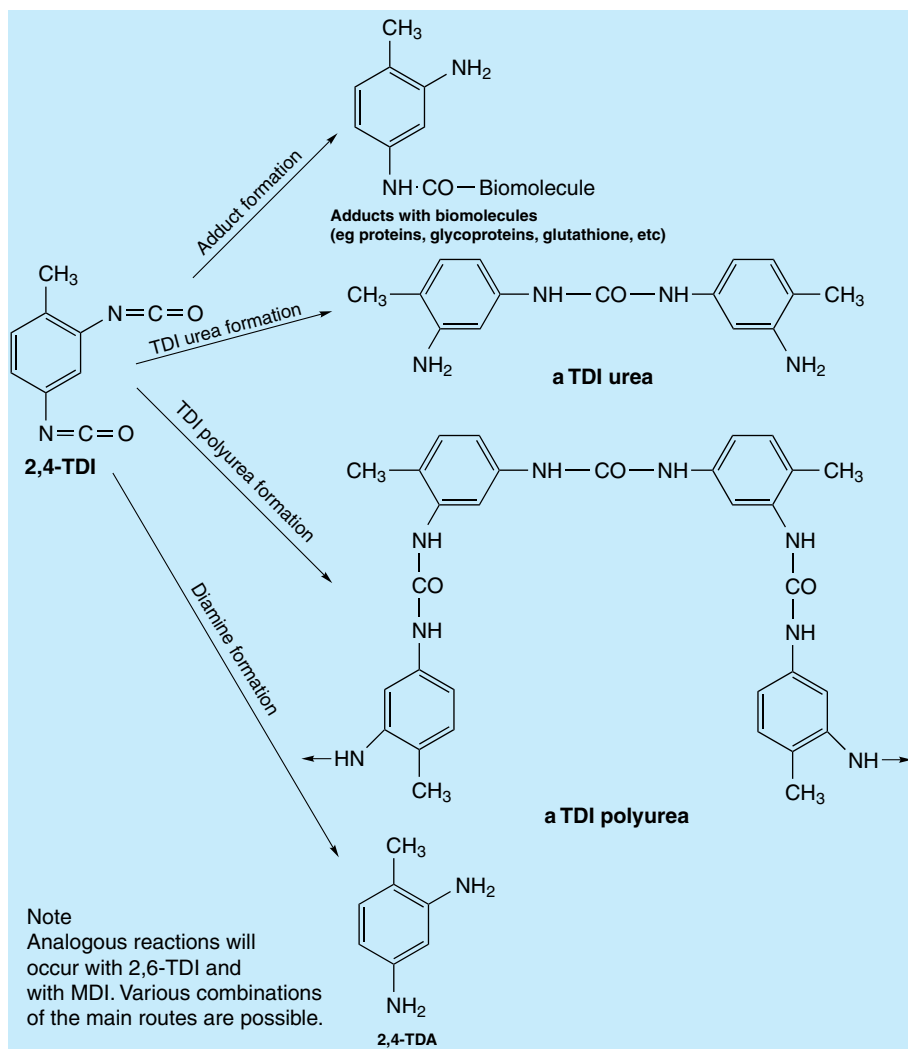
Figure 3.9 Competitive reaction pathways of TDI in biological systems

The hydrolysis of MDI and TDI to give the corresponding diamines is normally a very minor reaction under the conditions prevailing in the respiratory tract. If any diisocyanate is hydrolyzed, the amine produced will react rapidly with excess diisocyanate to produce ureas and polyureas. At concentrations normally found in workplace environments it is believed that the predominant reactions are those involving biomolecules such as proteins. The

$$R - NH_2 + O = C = N - R' \longrightarrow R - NH - CO - NH - R'$$

a urea

e.g.   lysine in proteins
          adenine in nucleic acids

$$R - OH + O = C = N - R' \longrightarrow R - O - CO - NH - R'$$

**a carbamate
(a urethane)**

e.g.   glycerol from fat
          serine in proteins
          carbohydrates

$$R - SH + O = C = N - R' \longrightarrow R - S - CO - NH - R'$$

a thiocarbamate

e.g.   cysteine in proteins
          glutathione

$$R - CO - OH + O = C = N - R' \longrightarrow R - CO - O - CO - NHR'$$

a mixed anhydride

e.g.   glutamic acid in proteins $R - CO - NH - R' + CO_2$

an amide
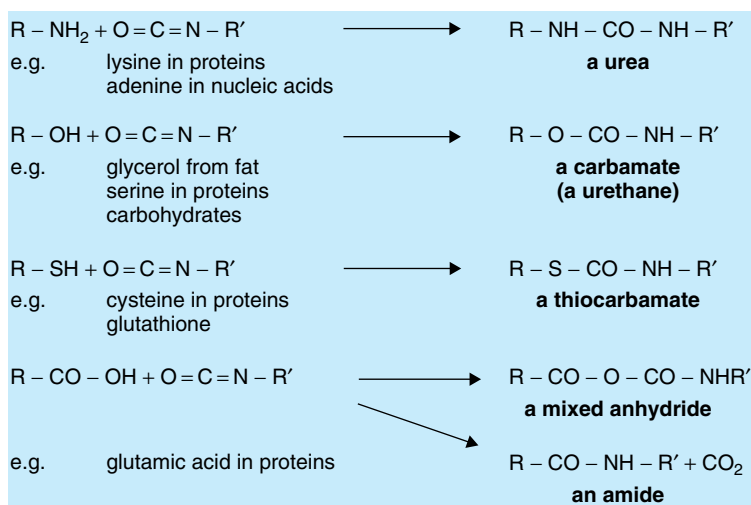
Figure 3.10 **Possible reactions of isocyanates with reactive functional groups in biomolecules**

reaction products (often called adducts or conjugates) are generally biologically inactive, and are removed from the body by normal metabolic processes. The exceptions are antigenic moieties involved in sensitization processes, discussed elsewhere.

This section contains a summary of the findings of many scientists who have worked with diisocyanates to understand how they can be absorbed and what happens to the molecules when they have been absorbed. The predominant route of human exposure in the workplace is by inhalation; the skin is also a potential route of exposure. Direct oral exposure is unlikely to occur. Therefore, animal studies where the material has been given by inhalation take precedence over studies where the oral route has been used.

Inhalation exposure
The extent of penetration and absorption via inhalation can vary depending on the physical state of the diisocyanate. TDI has usually been administered to animals as a vapour. Due to its extremely low vapour pressure, MDI has to be administered as an aerosol in animal studies to achieve sufficient concentration to cause biological effects. The standard in inhalation toxicology is to use very small aerosol particles which are respirable (less that 5 μm). This represents what is likely to be a *worst case* situation, and does not necessarily reflect real-life workplace situations. Diisocyanates are not absorbed unchanged in large quantities via inhalation. Reactions with biomolecules such as glutathione, mucopolysaccharides and proteins present in the moist environment of the respiratory tract are likely to occur before significant absorption takes place. In the respiratory tract the material can react either with biomolecules, or with moisture to form amines which themselves usually react rapidly with further diisocyanate to form ureas and polyureas (Kennedy *et al*., 1989).

Studies using the inhalation route of exposure have been carried out using radiolabelled MDI (Brown *et al*., 1993; CENS, 1976, 1977b) or TDI (Timchalk *et al*., 1994) to follow the molecule within the animal. In the respiratory tract

the reaction of the diisocyanate with biomolecules takes place very rapidly. Studies with TDI have shown that radiolabelled material is absorbed into the bloodstream and is found in a form bound to plasma macromolecules (Kennedy *et al.*, 1994). Estimates of the proportion of inhaled TDI absorbed into the blood range from 60 to 90 % (Timchalk *et al.*, 1994). TDI in the blood is essentially present in a conjugated form of relatively high molecular weight.

The reaction of diisocyanate with amino, hydroxyl or thiol groups present in biomolecules can theoretically occur, but with proteins the reaction with the amino groups seems to predominate and the material which is in the systemic circulation is in the form of diisocyanate irreversibly bound to protein. The large variety of possible reactions between MDI or TDI and functional groups on proteins forms the basis for a whole matrix of possible metabolites (Figure 3.11). Bifunctional isocyanates can lead to cross-linking both within molecules and between molecules, which again increases the number of possible products. Reactions with proteins are certainly the major pathways
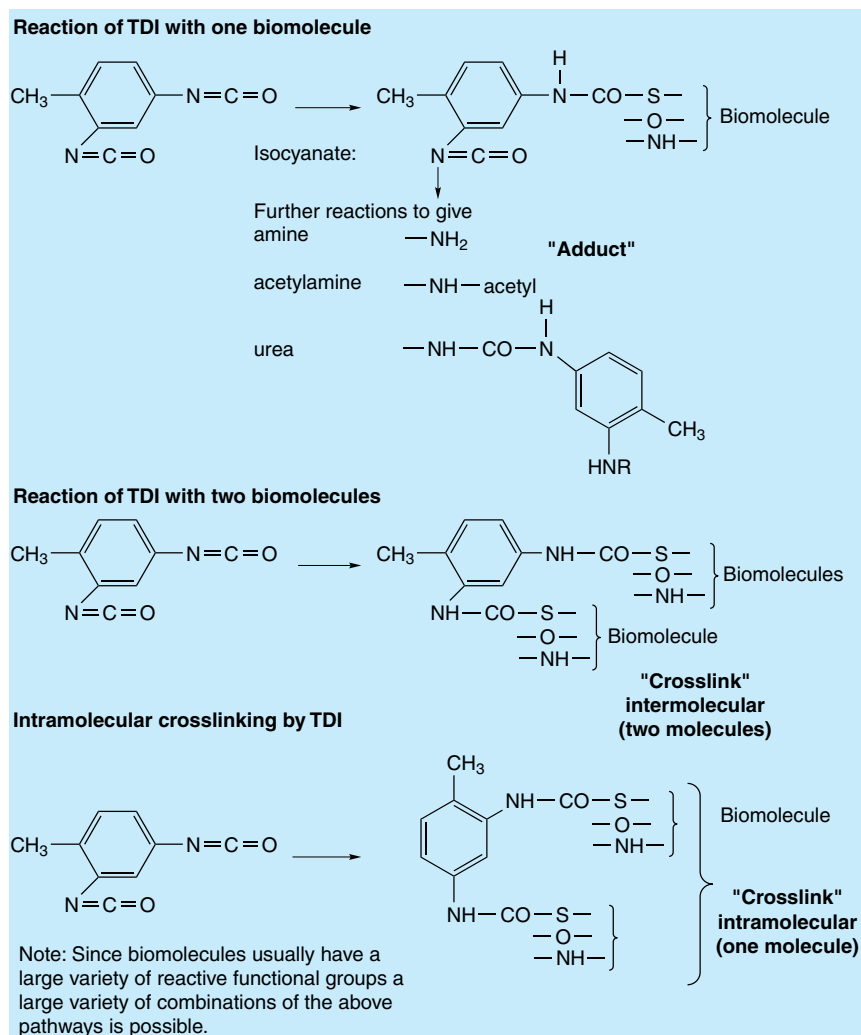

Figure 3.11   Possible reactions between 2,4-TDI and biomolecules

but this does not exclude reaction with sugar moieties in glycoproteins or with other biomolecules.

The amount of inhaled diisocyanate available to react with biological macro-molecules is insignificant compared with the total amount of macromolecules present and therefore in general it does not interfere with any biological processes requiring the macromolecules, and the impact on normal functions is minimal. It has been demonstrated that the amount of diisocyanate which is absorbed and bound in the blood is dependent upon the concentration and the duration of exposure (Kennedy *et al.*, 1994).

The bound diisocyanate is not available for simple metabolic degradation reactions, and this means that the formation of free parent amines is likely to be a minor pathway. As such, the diamine is therefore not available to become involved in biological processes. Breakdown products of these chemical conjugates are found in the urine. Analyses of the urine following radiolabelled diisocyanate exposure have shown that the urine has to be subject to aggressive chemical action such as acidic hydrolysis for the radioactivity originally associated with the diisocyanate to be released from the carrier molecule in the form of the diamine; no free diisocyanate has been detected.

Inhalation studies using radiolabelled TDI showed that, after exposure, radioactive material was excreted in both urine and faeces (Timchalk *et al.*, 1994; Kennedy *et al.*, 1994). There was no evidence for metabolic breakdown into exhaled carbon dioxide. 48 h after exposure the radioactivity in the urine, representing TDI that had been absorbed, amounted to some 15 % of the total radioactivity recovered. Analysis of urine samples from TDI-exposed animals showed that no free TDI was present, that over 90 % of the urinary metabolites existed as a conjugated form, and that a small amount of acetylated toluene diamine was also produced. Faecal elimination represented approximately 50 % of the recovered radioactivity 48 h after exposure. Radioactivity in the faeces may have originated from two sources. Diisocyanate that reacted with the components of mucus in the lung would have been cleared into the gastrointestinal tract by mucociliary clearance. Some absorbed and conjugated TDI could have been eliminated as breakdown products in the bile (CENS, 1977a; Kennedy *et al.*, 1989) and subsequently eliminated in the faeces. The remaining radioactivity at 48 h was found in the tissues and carcass, with about half of it in the gastrointestinal contents. Results with MDI were similar (CENS, 1977b).

Oral exposure

Studies on the absorption of TDI by the oral route have shown a different picture to that seen with inhalation. In the acidic environment of the stomach, reactions with water predominate to produce diamine. Some of the amine groups then react with molecules of diisocyanate to form polyureas.

With TDI administered orally over 48 h, free amine was detected in the urine. However, by this route the urine was a minor path of excretion (7 % of the dose) compared to the faeces (80 %). Where large doses were administered orally, macromolecules of polyurea were found in the stomach of experimental animals (Jeffcoat *et al.*, 1985). This route of exposure is obviously of little relevance to the understanding of the toxicology of diisocyanates because it is not a significant route in humans.

Dermal exposure

Most of the MDI and TDI applied to unbroken skin reacts with the skin; very little appears to penetrate into the body by this route. A study monitoring the elimination of radioactivity in urine and faeces following the application of a dose of radiolabelled 4,4′-MDI to the skin of rats, demonstrated that there was minimal absorption into the body. Following an exposure of duration 8 h, less than 1 % of the dose was excreted over the following 120 h, indicating that absorption into the blood circulation was extremely low (Leibold *et al.*, 1999).

Toxicology studies

Toxicological studies follow a stepwise approach in assessing the toxicology of chemicals, using a series of internationally agreed protocols. Laboratory animals are exposed to chemicals for increasing periods of time and to increasing concentrations from a single exposure up to lifetime exposure. In this way any potential effects of the chemical can be determined and predictions made about the effects of short-term exposure, mid-term exposure and long-term exposure of humans. The animals are subjected to a sophisticated array of assessments after the exposure periods which are designed to determine the range of toxic effects which may be expected and their dose–response relationships (Table 3.5).

Table 3.5   **Toxicity studies.**

Single exposure (acute)	**Route**
• Acute lethality	Oral, dermal, inhalation
• Irritation	Ocular, dermal, inhalation
• Sensitization	Dermal, inhalation
Repeated dose toxicity studies	**Route**
• 2 week	Oral, inhalation
• 90 day	Inhalation
• Lifetime	Oral, inhalation
Special studies	
• Absorption, distribution, metabolism, excretion	
• Genotoxicity	
• Developmental toxicity	
• Reproductive toxicity	

In addition, study designs have been developed to assess the effect of chemicals on reproduction and the development of offspring. A series of specialized investigations have also been carried out to determine whether a chemical can have any adverse effect on the genetic material within the cells.

Toxic effects after a single exposure: acute toxicity

Acute single-exposure toxicity studies are used to establish the potential toxicity of a material under defined laboratory conditions using different modes of exposure such as the oral, dermal or inhalation routes. *Worst case* conditions

Table 3.6   **Acute toxicity data.**

Study	Polymeric MDI		TDI	
	Result	**Reference**	**Result**	**Reference**
Oral LD_{50} (rat)	>19 000 mg/kg	Union Carbide (1982)	4130 mg/kg	Woolrich (1982)
Dermal LD_{50} (rabbit)	>19 000 mg/kg	Union Carbide (1982)	>16 000 mg/kg	Zapp (1957)
Inhalation LC_{50}, 4 h (rat)	490 mg/m^3 (respirable aerosol)	Reuzel *et al.* (1994b)	101 mg/m^3 (vapour)	Duncan *et al.* (1962)
Respiratory rate, RD_{50}, 4 h	32 mg/m^3 (mouse)	Weyel and Schaffer (1985)	1.4 mg/m^3 (rat)	Sangha and Alarie (1979)

LD_{50}: the single dose expected to cause death in 50 % of exposed organisms.
LC_{50}: the exposure concentration expected to cause death in 50 % of exposed organisms after a stated exposure period.
RD_{50}: the exposure concentration expected to cause a 50 % reduction in the respiratory rate due to sensory or respiratory irritation.

> In experimental toxicology, acute studies refer to a single administration with a holding period of usually up to 2 weeks. Chronic studies refer to repeated exposures over a significant fraction of the life span.

are applied in such acute tests and they provide useful reference points for evaluating the short-term effects of chemicals. Similar worst case conditions may not actually occur in human exposure. However, as all chemicals are assessed in the same ways, these studies form a ranking against which all chemicals can be considered for classification and labelling purposes. These studies also form the first step in determining doses for longer-term studies.

Acute toxicity data for MDI and TDI are shown in Table 3.6.

Single-dose (acute) toxicity effects of MDI

MDI has an extremely low vapour pressure, such that it is impossible to generate concentrations of vapour for a single inhalation exposure which approach those which may be toxic. The maximum theoretical concentration of 4,4'-MDI vapour at 20 °C (6.1 ppb) is approximately the long-term occupational exposure limit (5 ppb). Since some workplace exposure to MDI may be encountered as an aerosol, acute toxicity studies have been carried out using MDI as an ideal respirable aerosol. In order to maximize the possibility of a material causing toxicity, most studies using aerosols are carried out with these small particle sizes even though the particle sizes which may be encountered in the workplace may be considerably larger. To achieve a definite response, a worst case test atmosphere has often been used, with very fine respirable particles (less than 5 µm) suspended in air in order to maximize the delivery of MDI to the lung. Particles which are greater than 5 µm in diameter are unlikely to penetrate into the deep part of the lung (see Figure 3.1).

An acute inhalation study with respirable MDI aerosol was carried out according to a standard study design and gave an assessment of the acute toxicity of the MDI (Reuzel *et al.*, 1994b). At the highest concentrations there was direct lung damage which caused the death of some of the rats used in the study. The LC_{50} value for an exposure of 4 h to aerosols (95.5 % <4.3 µm) which was determined for MDI was 490 mg/m^3, which indicates moderate toxicity.

MDI did not cause toxicity in rats after a single oral dose administration even at the maximum dose which was required by the study guidelines (Wazeter

et al., 1964a; Bomhard, 1990). A review of the literature reveals that MDI has irritant effects to the skin and eye as determined in the rabbit (Woolrich, 1982; Duprat *et al*., 1976; Wazeter *et al*., 1964b).

Single-dose (acute) toxicity effects of TDI

TDI has also been the subject of acute inhalation toxicity studies, in which maximum doses could be achieved using vapour at high concentrations. At the highest concentrations used there was direct lung damage, which caused the death of some of the rats used in the study. LC_{50} values were determined for TDI; after an exposure of 1 h the LC_{50} was 480 mg/m^3 (66 000 ppb) (Doe and Horspool, 1980) and a value determined after an exposure of 4 h was 101 mg/m^3 (13 900 ppb) (Duncan *et al*., 1962). These figures demonstrate moderate toxicity. TDI did not cause any significant toxicity when given by the oral route even at the high doses required by the study design. A review of the literature shows that liquid TDI was irritating to the skin and the eye in rabbit tests (Duprat *et al*., 1976; Wazeter *et al*., 1964b).

Sensitization

Respiratory sensitization

Following the reports of asthma in humans caused by MDI and TDI within the occupational context, there has been extensive investigation of the mechanisms of these events in animal studies. However, no laboratory animal model is yet sufficiently robust to simulate all the parameters of human diisocyanate asthma. Because of this, there are no accepted animal tests for asthma. Investigators have been able to demonstrate the presence of antibodies to both MDI and TDI following inhalation in laboratory animals (Botham *et al*., 1988; Karol *et al*., 1980). The guinea pig has often been used as a test animal, and the antibodies detected are of the type which attach to cells in the lung and which can cause the release of substances that give rise to allergic reactions (mediators). The presence of antibodies, however, is insufficient to demonstrate asthma. Exposure of the animals to the diisocyanate alone has not consistently shown allergic reactions in the lung. However, in the case of TDI, if the diisocyanate was combined with a protein molecule (conjugated) and the guinea pigs inhaled the conjugate, then asthma-like reactions were seen (Karol, 1983). This is in contrast to other chemicals, such as trimellitic anhydride, which cause allergic asthma without mediation via a conjugate; these cause asthmatic or allergic reactions in the lungs of guinea pigs soon after first exposure (Kimber *et al*., 1996; Pauluhn and Mohr, 1994).

In the guinea pig, production of antibodies in response to inhaled diisocyanate shows a dose–response relationship, with a threshold concentration below which exposures do not give rise to antibody production. Karol (1983) showed that after an exposure of 3 h to 120 ppb TDI on five consecutive days, none of a group of guinea pigs had produced antibodies. Increasing exposure concentrations increased the numbers of animals responding and the strength of the response, until all of those exposed to 930 ppb had significant anti-TDI antibodies. Other workers have reported similar findings with TDI and polymeric MDI (Aoyama *et al*., 1994; Pauluhn and Dearman, 1997).

It has been shown that these antibodies can also be induced via topical contact (Rattray *et al*., 1994). Although very low amounts of diisocyanate

are required to induce antibodies when the chemical is injected *into the skin*, the concentration required to induce antibodies when the material is placed *on the skin* is high. It is not possible to extrapolate these results directly to humans, although they do underline that dermal contact with diisocyanates should be avoided. What role, if any, dermal contact plays in the induction of occupational asthma is under debate.

These results, generated in inhalation and topical application studies, have been the subject of much discussion amongst scientists because they do not reproduce the complete human asthma syndrome. Some theories suggest that diisocyanate asthma is not exclusively immunological in its cause, but may be due to a combination of various adverse effects on the respiratory tract. Certainly, to take the presence of antibodies as complete evidence of diisocyanate asthma is unjustifiable.

Skin sensitization

Standard animal tests for skin sensitization have been carried out with both MDI and TDI (Duprat *et al.*, 1976). These tests involve an induction stage in which the test material is applied to the shaved skin of the animal, or by injection just into the skin. A challenge stage follows in which the material is applied to the skin at a different site, and the sensitization response of inflammation, such as redness or skin swelling, is then assessed. Both MDI and TDI have been shown to be skin sensitizers in such tests.

Effects on the respiratory tract

The predominant effects of MDI and TDI are on the respiratory tract. This is likely to be due to the reactive isocyanate group reacting with the surface materials of the lung. The lining of the respiratory tract contains a number of detectors which are specialized nerve endings called receptors, the purpose of which is to detect the presence of harmful materials and change the breathing pattern to protect the individual. The presence of irritant materials in the upper respiratory tract of mice causes a decrease in breathing rate which can be related to adverse effects in humans. These adverse effects in humans range from a feeling of stinging and burning to a sensation of breathlessness. Both MDI and TDI have been assessed in mice and have been shown to cause a halving of the respiratory rate (RD_{50}) at concentrations of $32 \, mg/m^3$ for MDI in mice and $1.4 \, mg/m^3$ (200 ppb) for TDI in rats (Weyel and Schaffer, 1985; Sangha and Alarie, 1979). Humans find similar concentrations strongly irritating.

Toxic effects after repeated exposure: subchronic and chronic toxicity

Adverse health effects from prolonged repeated inhalation exposures to MDI or TDI are essentially confined to the respiratory tract. Both compounds are irritating to the airways, and can cause inflammation. At higher concentrations the effects can be severe.

In rodents, the effect of repeated exposure to chemicals is studied for approximately 2 years. Initially, exposure over 2 to 4 weeks is assessed, then in a further study the exposure time is extended to 3 months. The results of these studies are used both to estimate the effect of exposure to the material and to set dose levels for chronic studies which last for essentially the expected lifetime of the experimental animals, usually mice or rats. The aim of these 24 month studies is to assess the toxic potential over this considerable period of time and the potential of the chemical to induce tumours. Exposure times by inhalation are designed to mimic workplace scenarios of 6 h per day for 5 days per week.

MTD: maximum tolerated dose, the dose expected to produce limited toxicity, for example 10 % or greater retardation of body weight gain as compared with control animals.

It is very important to understand the philosophy of the setting of the exposure levels in chronic or 24 month studies. The top exposure level of a study is that judged to give a dose causing limited toxicity, and is known as the maximum tolerated dose (MTD). This ensures that the animals are exposed to the highest level which does not shorten their lifespan, but does produce an observable effect such as reduction in rate of body weight gain. This maximizes the chance of an adverse effect occurring. If, for example, no indication of carcinogenicity results, then there is a high degree of confidence that the test substance does not have the potential to cause cancer in humans at workplace exposure levels. However, if the top dose is too high and the chemical under test thereby causes prolonged tissue damage, then tumours may result which are not necessarily relevant to human exposure. Studies of this nature should be carried out using a relevant route of exposure, which in the case of the diisocyanates is inhalation, and require interpretation by experts.

Both MDI and TDI have been the subject of thorough evaluations in inhalation studies of up to 24 months' duration and all of these studies have indicated that the major effects of diisocyanates relate to their reactivity and their subsequent irritating effect on the respiratory tract, which is predicted from a study of their chemistry (Table 3.7).

Rats and mice were exposed to TDI vapour for 24 months (Loeser, 1983). They were exposed to concentrations of 50 and 150 ppb (0.36 and 1.1 mg/m^3) for 6 h a day for 5 days a week. At the higher exposure level, TDI caused some minor effects in rats, which were reduced body weight gain and chronic rhinitis. A similar picture was seen in mice at the top exposure level. These results indicate that both studies achieved an adverse effect and were valid. There were no adverse health effects at the lower concentration of 50 ppb (0.36 mg/m^3) in either species. There is a natural rate of occurrence of tumours of many types in animal groups, as there is in humans. There were no changes to this normal incidence or the type of tumours seen in either rats or mice at either dose level. These data show that TDI has no carcinogenic potential by inhalation under the conditions studied.

TDI has also been the subject of a chronic toxicity study in which the animals were dosed by the oral route (DHHS NTP, 1986). TDI dissolved in corn oil was dosed directly into the stomach of rats and mice. There were indications of an increase of some types of tumour in this study. There were also many premature deaths caused by poor techniques of administration of the test substance. In addition, it was established that the TDI degraded in the corn oil. It is known that oral dosing of diisocyanates is an irrelevant route of administration and therefore this study is regarded as being of no relevance to human health assessment, as well as being of very poor quality. The shortcomings

Table 3.7 **Chronic toxicity studies on MDI and TDI.**

	4,4′-MDI	Polymeric MDI	80/20 TDI	80/20 TDI
Route	Inhalation[a]	Inhalation[b]	Gavage[c]	Inhalation[d]
State	Respirable aerosol	Respirable aerosol	Liquid in corn oil	Vapour
Species	Rat	Rat	Rat and mouse	Rat and mouse
Sex	Female	Male and female	Male and female	Male and female
Dose levels	0, 0.2, 0.7, 2.1 mg/m^3	0, 0.2, 1.0, 6.0 mg/m^3	0, 60, 120 mg/kg (female rats and mice) 0, 30, 60 mg/kg (male rats) 0, 120, 240 mg/kg (male mice)	0, 50, 150 ppb
Exposure	17 h/day 5 days/week 20 months	6 h/day 5 days/week 2 years	Once a day 5 days/week 2 years	6 h/day 5 days/week 2 years
Maximum tolerated dose	Achieved	Achieved	Exceeded	Achieved
Histopathology	Nasal and pulmonary Tissue lesions	Nasal and pulmonary tissue lesions, tumours	Multiple site tumours	Nasal and pulmonary tissue lesions
No observed adverse effect level (NOAEL)	<0.21 mg/m^{3e}	0.2 mg/m^3 (19 ppb) (any adverse effect) 1.0 mg/m^3 (96 ppb) (tumours)[e]	<30 mg/kg (rat) <60 mg/kg (mouse)	<50 ppb (0.36 mg/m^3)

[a] Ernst *et al.* (1998).
[b] Reuzel *et al.* (1994a).
[c] DHHS NTP (1986).
[d] Loeser (1983).
[e] See Feron *et al.* (2001) for a combined review of studies *a* and *b*.

of the study have been reviewed in depth (Clement Associates, 1985; Ader *et al*., 1987). Despite the experimental deficiencies and irrelevance to normal human exposure, authorities use these data for formal reasons as evidence for carcinogenic potential and as a basis for the classification of TDI as an animal carcinogen.

MDI has been evaluated in a series of inhalation studies in rats ranging in duration from 2 weeks to 24 months (Reuzel *et al*., 1994a, 1994b). Polymeric MDI was the test substance in all these studies and the animals were exposed to respirable aerosols less than $5\,\mu$m in size, which ensured that the particles penetrated deep into the lung. In the 2 week studies there were severe effects on the lung at the high exposure level of $14\,mg/m^3$. The effects were less severe at $5\,mg/m^3$ per day and they were almost absent at $2\,mg/m^3$. In studies lasting 13 weeks the effects were again confined to the respiratory tract with severe effects at $12\,mg/m^3$ but minimal changes at $4\,mg/m^3$. There were no effects at $1\,mg/m^3$.

On the basis of these results exposure levels of 0.2, 1 and $6\,mg/m^3$ (93.5 % of the particles were less than $4.2\,\mu$m) were selected for a 2 year study. The main effects were upon the respiratory tract of the rats exposed to the top level. There was evidence of chronic irritation and a small increase in the number of rats with tumours in the lung when compared with unexposed control animals. These tumours are regarded as being the consequence of the irritant and inflammatory properties of polymeric MDI at this extremely high level. It is considered that exposure of humans to levels which do not cause recurrent damage will not produce tumours and the other lung effects. There were less severe effects (reversible nasal lesions) and no tumours in the lungs of rats exposed to $1.0\,mg/m^3$ and there were no adverse health effects at $0.2\,mg/m^3$ over the lifetime of the animals.

Similar results were seen in another study in which rats were exposed to 4,4′-MDI for the unusual duration of $17\,h$ a day at concentrations of 0.2, 0.7 and $2.0\,mg/m^3$. The longer duration of exposure was chosen to mimic the period of exposure which might be encountered in a domestic situation, although it is very difficult to envisage a situation in which MDI particulates would ever be generated in the home. Indeed, generation of high concentrations of respirable particulates of MDI, which can induce lung lesions comparable to those seen in the rat studies, would be difficult to achieve outside the laboratory. The results of this study were very similar to those from the polymeric MDI study which used $6\,h$ a day for the exposure period, with effects again confined to the respiratory tract. There was chronic irritation and inflammation of the respiratory tract and, although some preneoplastic changes were evident, there was no increased incidence of pulmonary tumours at any exposure concentration (Ernst *et al*., 1998).

A comparative analysis of the pathology findings from these two studies concluded that the results could be combined, and that $0.19\,mg/m^3$ (exposure conditions $6\,h/day$, 5 days/week for 24 months) could be considered as a no-effect level for both monomeric and polymeric MDI (Feron *et al*., 2001).

In all of these inhalation studies with TDI or MDI there were no effects on any other organs or systems of the body, apart from those noted in the respiratory tract and the lymph nodes associated with the respiratory tract. In particular, there were no indications of adverse effects on the nervous

system, reproductive organs or general organ systems (liver, kidney, etc.) of the test animals.

Genetic toxicology

> **The assessment of all the available data indicates that MDI and TDI have no significant mutagenic potential.**

Genetic toxicity is the term used to describe adverse effects on the genetic information stored in molecules of deoxyribonucleic acid (DNA) in chromosomes within the nucleus of cells. Genetic toxicology studies are used to predict whether a chemical may have a potential to cause cancer or other diseases linked to damage to the genetic material. In addition, these studies can help to explain and put into context other results such as those from long-term studies. A validated cascade of tests has been developed to evaluate the effect of chemicals on the genetic material.

> Genotoxicity describes the action of a chemical reacting directly with the genetic material, or DNA. This may be detectable as simple chemical adducts, or as gross changes in chromosome structure. Mutagenicity is the process of creating a change to the DNA that can be passed on to the next generation of cells or organisms (for example, bacteria or animals) as mutations.

The tests usually start with *in vitro* systems using bacterial cells, such as in the bacterial reverse mutation test (Ames test). This test typically uses Salmonella bacteria which have been modified so that they cannot survive in the absence of a certain nutrient. In the presence of a mutagenic or genotoxic chemical the cells revert to their original state and no longer need the supplemental nutrient to grow. A mutation caused by the test chemical is indicated by growth of colonies of bacteria in a depleted medium.

There have been a number of assays using MDI or TDI in this system and the results are at first sight quite confusing. In some studies MDI and TDI have been reported to cause mutation and in other studies they have been found to be without effect. When the results of these studies have been considered very carefully it has been discovered that in the positive studies the MDI or TDI has been added in a water-soluble organic solvent to solubilize the material and to facilitate dispersion in the aqueous test system. However, the use of specific solvents, such as dimethylsulphoxide in particular, profoundly increases the rate of hydrolysis to the diamine (Gahlmann *et al.*, 1993). Studies using dimethylsulphoxide as solvent are often, in effect, studies of the respective diamines and are therefore of little relevance to diisocyanates as encountered by inhalation. The diamines are known to be mutagenic in this assay. Observed mutagenicity test results on both MDI and TDI can be explained by their hydrolysis and further reactions in the presence of solvents or test media (Seel *et al.*, 1999). It has been shown that when MDI is used in the assay in a solvent in which hydrolysis is slow, it is not mutagenic (Herbold *et al.*, 1998).

In vitro assays cannot completely reproduce the fate of chemicals in whole animals. *In vitro* studies do not mimic all of the metabolic reactions which can take place *in vivo*. Although enzyme preparations are included with these

assays, *in vivo* studies also test whether the chemicals reach the DNA. A series of assays has been developed to determine whether or not chemicals have the ability to cause damage to the genetic material in whole animals. The unscheduled DNA synthesis (UDS) assay detects the repair or synthesis of new DNA molecules which might be expected following damage. TDI has been examined for its capability to cause UDS in both the liver and the lung and was found to be without activity in both types of tissue following exposure by inhalation (Benford and Riley, 1988). Another assay which has been developed is the mouse micronucleus assay which assesses the effect of chemicals on the chromosomes in the blood-forming elements in the bone marrow. Both MDI and TDI administered by inhalation (Pauluhn *et al*., 2001; Mackay, 1992; Loeser, 1983) have been found to be negative in this assay.

Interaction between the test material and DNA in the form of covalent binding is seen as a key event in genetic toxicology. MDI has been the subject of a detailed evaluation of its capability to combine covalently with DNA *in vivo*. These investigations were carried out in parallel with a long-term inhalation study which was referred to earlier (Vock *et al*., 1996). Tissues from the nose and the lung of these animals were examined for the presence of adducts of MDI with DNA. The results indicated that MDI did not react with DNA in these tissues to any degree and was therefore unlikely to cause any genetic damage. In addition the DNA-binding potential of dermally applied MDI has been investigated. The level of MDI binding to DNA in either the skin at the site of application or internal organs was not sufficient to indicate a genotoxic threat (Vock *et al*., 1995; Vock and Lutz, 1997). Despite the most sophisticated experimentation, the data indicate that the MDI is only marginally active, if at all.

There are some research reports that suggest that both MDI and TDI may damage DNA. These studies have used novel techniques and cells grown in culture (Marczynski *et al*., 1992; 1993; Mäki-Paakkanen and Norppa, 1987). However, work by Vock *et al*. (1998) has shown that changes to DNA seen in cells exposed to MDI in culture are found only at exposure levels that are causing generalized toxicity to the cells, and are a consequence of the death of the cell through cytotoxicity (apoptosis). The DNA changes are not a specific and unique interaction with the cellular DNA, and these data again indicate that MDI is not genotoxic. These data support the view that tumours produced at the top concentration of MDI only in the inhalation study are not caused by a genotoxic mechanism, and are probably due to recurrent lung tissue damage.

Reproductive toxicology

There has been no observation or demonstration of adverse effects on reproduction due to either MDI or TDI.

The assessment of whether a chemical can cause adverse effects on reproduction is of importance in general toxicological evaluations. Studies can be designed to cover the full reproductive cycle, assessing whether the parents are capable of producing offspring, and evaluating in detail the development of the offspring. There are two major study designs which are used:

- The *developmental toxicity* study is a detailed investigation of the effect of exposure during pregnancy on the developing foetus.
- The *multi-generation* study is one in which parents are exposed before mating, and during gestation, and the offspring continue to be exposed as they mature. The offspring themselves become parents once they have reached sexual maturity and their offspring are exposed until they become mature. In this way the whole of the reproductive cycle is evaluated.

Developmental toxicity studies have been carried out on both MDI and TDI (Table 3.8). TDI has been the subject of evaluation by inhalation for potential effects on reproduction. Overall, there were no effects observed as might be expected with material whose only site of action is the respiratory tract.

Table 3.8   **Developmental toxicity studies on rats using MDI and TDI.**

	4,4′-MDI[a]	**Polymeric MDI[b]**	**TDI[c]**
Exposure	Inhalation of respirable aerosol	Inhalation of respirable aerosol	Inhalation of vapour
Concentration (mg/m^3)	0, 1, 3, 9	0, 1, 4, 12	0, 0.14, 0.7, 3.6
NOAEL foetal and maternal toxicity (mg/m^3)	3	4	0.7
Teratogenicity	None detected	None detected	None detected

[a]Buschmann *et al*. (1996).
[b]Gamer (1995).
[c]Tyl *et al*. (1999a).

Pregnant rats in a developmental toxicity study (Tyl *et al*., 1999a) were exposed to 80/20 TDI vapour at concentrations of 0, 0.14, 0.7 and 3.6 mg/m^3 (0, 20, 100 and 500 ppb) for 6 h a day on days 6 to 15 of pregnancy. This is the period during pregnancy when the foetus is forming its major organs and is the period of time when the foetus is most sensitive to the adverse effects of chemicals. As with other toxicological studies, the study was designed so that there was some adverse effect on the mothers at the top dose, which ensured that a rigorous assessment of toxicity was made. In this study, toxicity to the mothers was observed in the highest dose group with the signs being the reduction of body weight and food consumption. All of the litters developed normally at this exposure level, but there was an indication that the development of the foetuses had been marginally delayed by the toxicity shown in the mothers. This is a common finding in such studies and is not indicative of a specific sensitivity of the foetuses to the chemical. At the lower doses where there was no maternal toxicity, there were no effects observed on the foetuses.

MDI has been the subject of two developmental toxicity studies, with similar results. In the first study pregnant rats were exposed to respirable aerosols of polymeric MDI for 6 h a day on days 6 to 15 of pregnancy at concentrations of 1, 4 and 12 mg/m^3. In the mothers in the highest dose groups, the signs of toxicity observed were reduction of body weight, reduction in food and

water consumption and effects on the respiratory tract (Gamer *et al.*, 2000). Some extreme cases even included mortality at $12\,mg/m^3$. As with TDI, in the presence of the severe maternal toxicity, there was evidence of a slight delay in foetal development. This is not considered to be a specific effect on reproduction but a consequence of the toxicity seen in the mothers. The foetuses from the mothers exposed to 1 or $4\,mg/m^3$ developed normally. No birth defects were observed at any concentration level.

A second study with respirable aerosols of 4,4′-MDI (Buschmann *et al.*, 1996) used the same exposure regime at concentrations of 1, 3 and $9\,mg/m^3$. Maternal toxicity was seen as a decrease in the rate of weight gain during exposure and reduced food consumption. There were no other adverse effects. At the top dose there was an apparent increase in spontaneous changes in the foetuses, which fell within the range of background variation. There were no adverse effects observed at 1 or $3\,mg/m^3$.

These studies evaluated in detail the effect of diisocyanates on the developing foetus. Further investigations have also been made on the effects of MDI and TDI on the reproductive tract, and of TDI on the complete reproductive cycle. Neither MDI nor TDI showed any effects on the reproductive systems of animals exposed to these chemicals for up to 2 years. This has been ascertained by completion of a thorough histopathological assessment of both male and female reproductive systems. TDI has been evaluated in a complete life cycle (multigeneration study) (Tyl *et al.*, 1999b). The potential of TDI vapour to cause adverse effects across two reproduction cycles was studied at levels of 20, 80 and 300 ppb TDI (0.15, 0.6 and $2.2\,mg/m^3$) for 6 h a day. The study design called for evidence of toxicity in the parents to ensure that a rigorous evaluation was made and in this study there was evidence of irritation of the respiratory tract (rhinitis) at 20 ppb ($0.15\,mg/m^3$) and above in males, and 80 ppb ($0.6\,mg/m^3$) and above in females. There were no effects of TDI on the number of animals who became pregnant or the size of the litters or the number of pups which survived to maturity in any of the generations.

Diagnosis of diisocyanate asthma

These Appendixes have been written by David I. Bernstein, M.D., Associate Professor of Medicine, University of Cincinnati, USA. They have been provided to give direction to primary care physicians who are asked to evaluate workers for occupational asthma caused by exposure to diisocyanates.

Appendix 1

A guide for the primary care physician

The step-wise approach to the diagnosis of occupational asthma is complex. Therefore, a physician should be consulted who is experienced in the evaluation of occupational lung disorders. This diagnostic guide in the form of an algorithm has been designed for those situations in which such consultants are

not available. Adherence to the steps detailed will greatly increase the likelihood of an accurate diagnosis. The ability to adhere strictly to this protocol may depend on available resources for testing. However, a deviation from this protocol could result in an erroneous diagnosis.

Because this protocol relies on the serial measurement of lung function during active exposure to diisocyanates, this approach is applicable only for workers who are able to remain at work during the evaluation. It is useless for those who have already left the workplace. If possible, assessment of personal diisocyanate exposure using reliable analytical methods should be performed concurrent with clinical evaluation of the worker. This could allow correlation of diisocyanate exposure with work-related symptoms and changes in lung function.

Guidelines for confirming diisocyanate-induced asthma are presented in Figures 3.12 and 3.13. Both figures are explained in detail later.

Step 1	History of diisocyanate-induced occupational asthma
Step 2	Spirometry pre/post-bronchodilator
Step 3	4 weeks serial PEFR studies: 2 weeks at work and 2 weeks away
Step 4	Methacholine inhalation test after 2 weeks at work

Proceed to Step 5 (figure 3.13)
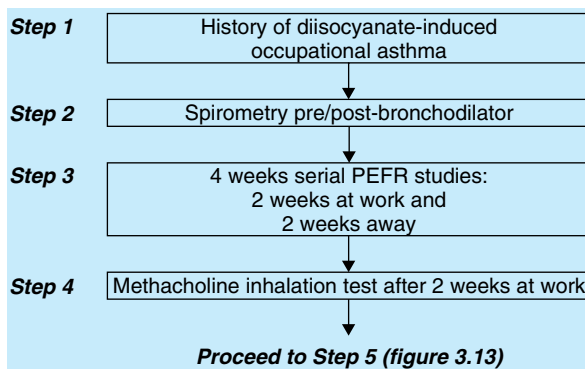
Figure 3.12   **Diagnostic testing for diisocyanate asthma**

Step 5

(a)	(b)	(c)	(d)	(e)
PEFR (−) meth (−)	PEFR (−) meth (+)	PEFR (+) meth (−)	PEFR (+) at work; meth (+)	PEFR (+) at work/home; meth (+)

No asthma

cessation of work for 6 months: evaluate monthly

| approve return to work: follow every 6 weeks | approve return to work: follow every 1 month | **Occupational asthma** | *improve* | *no change* |

no exposure to diisocyanates

Non-occupational asthma?

consult specialist
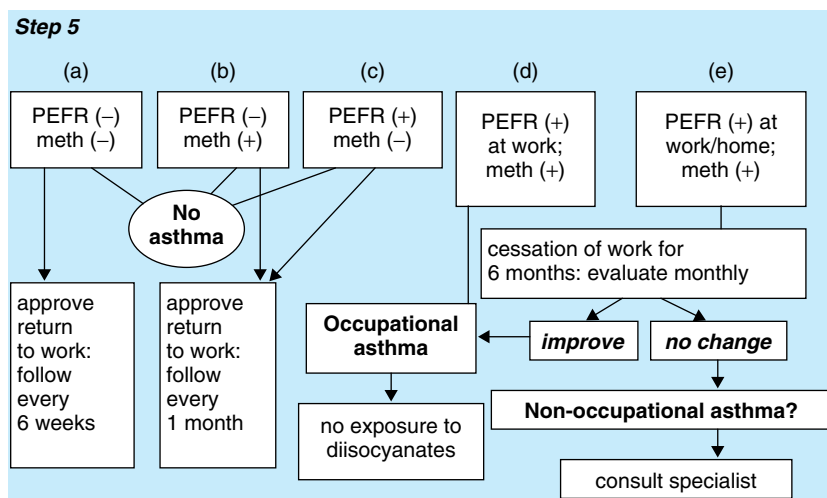
Figure 3.13   **Diagnosis and intervention**

Step 1: occupational history

Although a positive history of occupational asthma alone is not a specific method for accurate identification of occupational asthma caused by diisocyanates (Malo *et al*., 1991), it is an essential first step. An occupational respiratory questionnaire follows this text in *Appendix 2*: it can be used by the physician to capture relevant information pertaining to work-related asthmatic symptoms. Workers complaining of coughing, shortness of breath, wheezing or chest tightness which increase during or after the work shift should undergo further testing to confirm or exclude a diagnosis of occupational asthma. When completing the occupational history, the investigator must be aware of three different patterns of work-related asthmatic reactions: (1) an early asthmatic reaction that begins within 1 to 2 h at work and lasts 2 to 4 h; (2) a dual asthmatic reaction that includes an early asthmatic response followed by a late phase asthmatic reaction that begins after 4 to 12 h at work; (3) an isolated late phase asthmatic reaction that begins 4 to 12 h after beginning the work shift. These and other patterns of asthmatic reactions to diisocyanates are illustrated in Figure 3.14 (Perrin *et al*., 1991).

Using this knowledge, the examining doctor should be aware that some workers with occupational asthma may report that lower respiratory symptoms begin at work whereas other workers may not experience symptoms until after completion of the workshift. Asthmatic symptoms associated with late onset asthma can persist for days or even weeks after a single diisocyanate exposure (Cartier and Malo, 1993). However, most workers with occupational asthma report improvement at the weekend or during vacation.

Step 2: spirometric testing

A diagnosis of occupational asthma must be confirmed objectively in any worker complaining of chronic or intermittent cough, chest tightness, wheezing or dyspnea. First, it is important to investigate such workers for reversible airway obstruction. Simple spirometric testing should be performed before and after two to four inhalations of a fast-acting β_2-agonist (for example, albuterol) delivered by a metered dose inhaler. An increase in FEV_1 of at least 12 % after bronchodilator treatment establishes reversible airways disease or asthma (American Thoracic Society, 1993). **Failure to demonstrate reversible airway obstruction on a single test day does not exclude asthma. Regardless of whether there is demonstrable reversibility in FEV_1, all workers reporting lower respiratory symptoms must proceed to Step 3 for serial monitoring of lung function both at and away from work, followed by a methacholine inhalation challenge test (Step 4).**

Step 3: serial monitoring of lung function

When carefully supervised, serial monitoring of lung function as peak expiratory flow rate (PEFR) while at work is equivalent to a workplace challenge test.
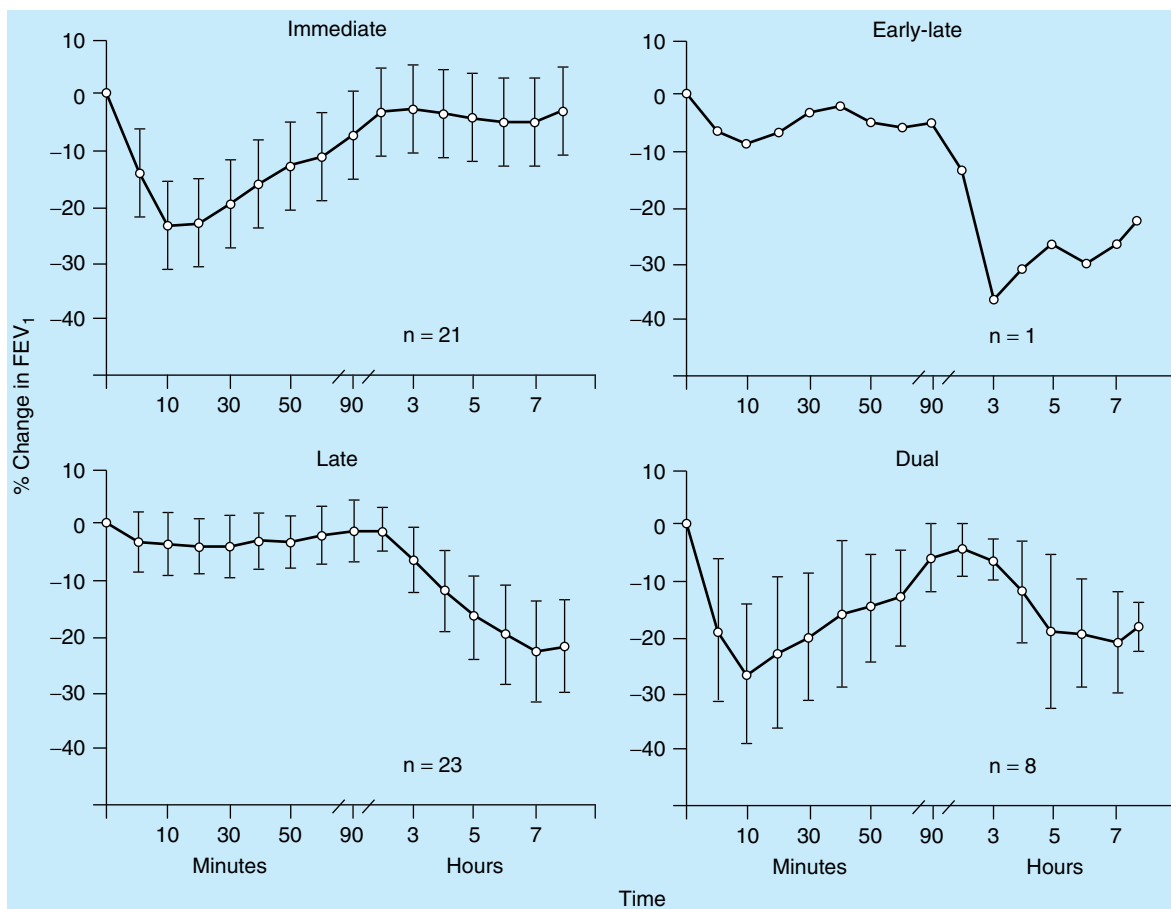
Figure 3.14   **Patterns of asthmatic reactions to diisocyanates (from Perrin *et al.*, 1991). Four typical patterns of asthmatic reactions after inhalation of MDI: (a) early bronchoconstriction that begins within minutes, lasting 2 to 3 h; (b) a delayed early reaction beginning 1 to 2 h after exposure; (c) an isolated late phase reaction with onset 3 to 5 h after MDI exposure; and (d) a dual phase asthmatic reaction characterized by an early and late phase response. Reproduced by permission from *Journal of Allergy and Clinical Immunology*, 87. pp. 630–639. Harcourt Health Sciences, Orlando, FL, USA**

Because there is potential risk in exposing a worker to a substance capable of triggering acute bronchoconstriction, baseline lung function must be adequate and asthma must be clinically stable for at least 1 week prior to testing. Thus, serial monitoring of PEFR at work should be performed only in workers who have a pre-test FEV_1 of $\geq 70\,\%$ of that predicted. Those workers who report previous severe work-related bronchospastic episodes and/or have an FEV_1 $< 70\,\%$ of that predicted should be referred to a consultant experienced in the evaluation of occupational asthma. Workers with concomitant medical conditions such as congestive heart failure and who are medically unstable should not be considered for this approach.

Measurement of intra-shift decrements in FEV_1 is an alternative to serial PEFRs for confirming work-related airway obstruction. However, FEV_1 performed before and after the workshift on several days is far less sensitive than

serial measurement of PEFRs performed every 2 to 3 h. An intra-shift or cross-shift decrease of $\geq 15\%$ during weeks at work (i.e. two to three times per week), but not during weeks away from work, signifies the presence of work-related airway obstruction. Failure to demonstrate intra-shift or cross-shift changes in FEV_1 does not exclude occupational asthma nor does it obviate the need to perform serial measurements of PEFR.

To obtain quality PEFR data, workers must be properly trained in the use of a portable peak flow rate meter, and the necessity to obtain a maximal forced expiratory effort must be emphasized. Worker instructions and PEFR schedules are provided after this text. PEFR measurements should be performed by symptomatic workers for 2 weeks at work (in a work area where a diisocyanate is being used) and during 2 to 4 weeks completely removed from exposure. PEFRs every 3 h during waking hours and if the subject is awakened during sleeping hours are to be recorded in diaries (*Appendix 3*). At least four daily readings are required. Once peak flow recordings have been collected, values (litres/minute) should be plotted on the *Y*-axis versus time on the *X*-axis (see Figure 3.15).
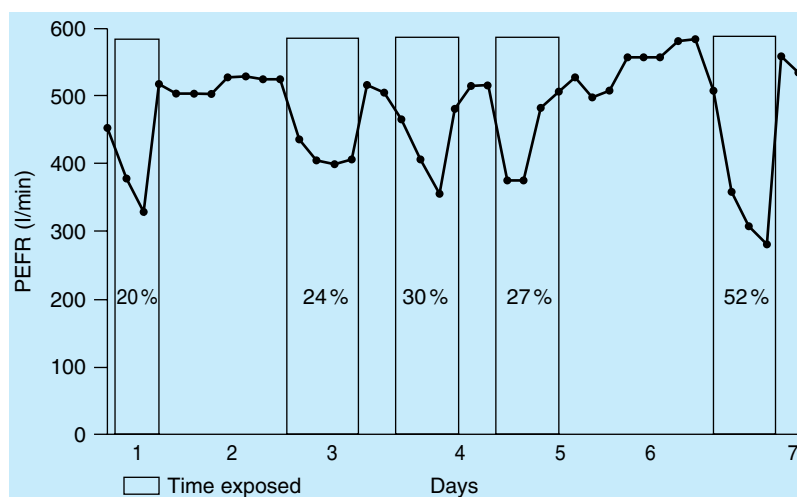
Figure 3.15 **Record of peak flow rates. Plot of a serial PEFR record obtained from a worker with occupational asthma shown as time in days versus the peak expiratory flow rate (l/min). The record demonstrates significant declines in PEFR from pre-exposure baseline values on workdays with exposure. (Smith** *et al.***, 1990)**

Non bronchodilator asthma medications, including inhaled corticosteroids and cromolyn, should not be withdrawn during PEFR monitoring. If deemed safe by the physician, regularly administered ß₂-agonist bronchodilators (for example, albuterol) should be used only on an as needed basis for acute bronchospasm. Recordings obtained during acute asthma exacerbations or viral infections which can cause decrements in lung function should not be included in the analysis.

Ideally, two experienced physicians blinded to the medical history of the worker should interpret the 4 week PEFR graphs by visual inspection.

Consistent intra-shift decreases in PEFR of $\geq 20\%$ compared to measurements obtained on days away from work are characteristic of occupational asthma. The absence of increased daily variability in PEFR [(maximum − minimum)/(maximum value × 100)] of $\geq 20\%$ on work days is incompatible with a diagnosis of occupational asthma. Significant decreases in PEFR both during work and during nonworking days, are usually consistent with nonoccupational asthma, although this pattern can occasionally be seen in workers with occupational asthma.

Step 4: methacholine testing

A methacholine inhalation challenge test defines the presence or absence of hyperreactive airways or nonspecific bronchial hyperresponsiveness. Methacholine testing is performed routinely in many physicians' offices and in pulmonary function laboratories. Nonspecific bronchial hyperresponsiveness, defined by a positive methacholine test, is a universal feature of persistent asthma with airway inflammation but can also be detected in a variety of nonasthmatic conditions such as chronic bronchitis, congestive heart failure and atopy.

The methacholine test is performed by having the patient inhale nebulized saline, which is followed by inhalation of incremental doses of methacholine (0.125 to 25 mg/ml) every 5 to 10 min until a 20 % decline from the post-saline FEV_1 is observed or until all challenge doses have been delivered without any decrease in the FEV_1. A positive response is defined as a 20 % decrease in FEV_1 after inhalation of a provocative concentration (PC_{20}) of ≤ 10 mg/ml of methacholine (Cockcroft *et al.*, 1992).

It is expected that not all physicians using these guidelines will have access to methacholine testing. This test is unnecessary in a worker in whom reversible airway obstruction has already been detected in Step 3. The methacholine test is recommended in symptomatic workers for its value in validating results of the PEFR studies. For the purpose of confirming or excluding occupational asthma, it is essential to perform methacholine testing:

(1) during work hours or within 1 h after leaving the workplace because airway reactivity can normalize within 2 to 3 h after leaving work (Durham *et al.*, 1987);
(2) after continuous work exposure to diisocyanates for at least 2 weeks; and
(3) on the last day of the work week.

A methacholine test is positive if the provocative concentration that elicits a 20 % decrease in FEV_1 (PC_{20}) from the saline baseline challenge is ≤ 10 mg/ml of methacholine chloride. A positive test will validate abnormal PEFR studies. On the other hand, a normal methacholine test ($PC_{20} > 10$ mg/ml) would exclude current asthma and validate normal PEFR studies, or invalidate abnormal PEFR measurements collected by the worker. If the methacholine test is normal and the PEFR results abnormal, poor technique or falsification of PEFR data must be suspected.

Step 5: diagnosis and intervention

As shown in Figure 3.12, Steps 1, 2 and 3 have led to five possible combinations of test results among symptomatic workers. Suggested interventions for diagnoses derived from results of methacholine and PEFR tests are shown in Figure 3.13 and are described below:

(a) *Normal PEFR studies and a negative methacholine test at work.* Such workers do not have asthma and can continue to work but should be re-evaluated every 6 months for as long as they continue to work with diisocyanates and experience symptoms.

(b) *Normal PEFR studies and a positive methacholine test.* It is likely that the worker has increased airway responsiveness and no asthma. Therefore, if such workers are allowed to return to work, monthly spirometry should be conducted by trained personnel before, during and after several work shifts during which diisocyanates are being used. The absence of intra-shift decreases in FEV_1 ($\geq 10\%$) excludes occupational asthma.

(c) *Abnormal PEFR studies and a negative methacholine test.* It is unlikely that the worker has asthma. As already mentioned, poor technique in performance of the PEFR test or poor reporting of PEFR data could account for these anomalous results. Such workers can sent back to work, with caution. However, careful monthly follow-up tests should be performed with intra-shift determinations of FEV_1 (see Step 5b) for as long as it is clinically indicated.

(d) *Abnormal PEFRs that decrease at work and improve away from work combined with a positive methacholine test.* These results confirm occupational asthma. Such individuals should be excluded completely from future exposure to diisocyanates. Following cessation of diisocyanate exposure, periodic assessment of FEV_1 and asthma symptoms is recommended in order to determine long-term treatment requirements and overall improvement in asthma.

(e) *Abnormal PEFR changes both at work and away from work and a positive methacholine test.* This situation presents a unique clinical challenge. Such individuals with continuous asthma may have either nonoccupational asthma or chronic occupational asthma. Because, in rare cases, improvement in occupational asthma and lung function may not be determined for months following cessation of exposure to diisocyanates, it is recommended that all workers with abnormal PEFR studies be totally excluded from exposure to diisocyanates for 6 months. Monthly evaluations for clinical symptoms, asthma medication requirements and FEV_1 are recommended. Gradual improvement in lung function and symptoms confirms occupational asthma and such workers cannot be re-exposed to diisocyanates. Failure to show improvement after a prolonged absence from work exposure is more consistent with nonoccupational asthma. However, a physician knowledgeable in occupational lung disease should be consulted to decide whether to allow such a worker to return to a department or processes that involve diisocyanates.

Appendix 2

MEDICAL SURVEY FORM

DEMOGRAPHICS AND EMPLOYMENT HISTORY

INSTRUCTIONS TO EMPLOYEE: PLEASE FILL IN OR CHECK
APPROPRIATE SPACE.

DATE:____/____/____

EMPLOYEE IDENTIFICATION

LAST NAME:_____

FIRST NAME:_____

ADDRESS:_____

CITY:_____STATE:_____ZIP:_____

DATE OF BIRTH:_____AGE:_____

PERSONAL DATA

1. HOME TELEPHONE:_____

2. ETHNIC BACKGROUND: WHITE   BLACK   HISPANIC   ASIAN

3. SEX: MALE   FEMALE

4. HEIGHT:_____

5. IF FEMALE, ARE YOU PREGNANT? YES_____ NO_____

6. HAVE YOU BEEN TRANSFERRED FROM A JOB FOR A HEALTH
    REASON?   YES_____NO_____

    IF YES, GIVE DETAILS:

    _____

    _____

    _____

7. WHAT IS YOUR USUAL SHIFT?

    _____

8. WHAT SHIFT ARE YOU WORKING PRESENTLY?

    _____

9. HOW LONG HAVE YOU BEEN AT YOUR CURRENT JOB?

    _____

10. WHEN DID YOU FIRST BEGIN WORKING IN YOUR CURRENT
    DEPARTMENT?

    _____

OCCUPATIONAL HISTORY

1. WHAT IS YOUR CURRENT WORK AREA?

    1A. WHAT PERCENT OF THE TIME ARE YOU IN YOUR AREA?

    _____%

2. WHAT IS YOUR CURRENT JOB DESCRIPTION?

3. LIST CHEMICALS OR OTHER SUBSTANCES WHICH MAY BE
    USED IN YOUR WORK AREA DURING A TYPICAL WORK
    WEEK:

Substance	How are you exposed?	Year started	Year ended

4. DATE YOU STARTED IN YOUR CURRENT JOB:

    _____/_____Month/Year

5. DESCRIBE PREVIOUS JOBS AT YOUR CURRENT PLACE OF
    EMPLOYMENT. Please begin with your most recent job and end
    with your first job. (Do not list current job.)

Department   Job   Year Started   Year Ended   Years on Job

_____

_____

_____

6.   DESCRIBE PREVIOUS JOBS STARTING WITH YOUR LAST JOB:

Department   Job   Year Started   Year Ended   Years on Job

_____

_____

_____

MEDICAL INTERVIEW

7.   WHILE AT YOUR CURRENT JOB, HAVE YOU HAD:

CHEST TIGHTNESS   YES_____ NO_____

WHEEZING   YES_____ NO_____

COUGH   YES_____ NO_____

SHORTNESS OF BREATH YES_____ NO_____

IF "YES" TO ANY OF ABOVE, ANSWER QUESTIONS 8–18

8.   DO THESE SYMPTOMS BEGIN IMMEDIATELY AFTER START-ING WORK (LESS THAN 1 HOUR)?   YES_____NO_____

9.   DO THESE SYMPTOMS BEGIN MORE THAN 1 HOUR AFTER STARTING WORK?

        YES_____NO_____

10. IF YES, HOW MANY HOURS?_____

11. HOW MANY HOURS DO THESE SYMPTOMS LAST WHILE AT WORK?_____

12. DO THESE SYMPTOMS CONTINUE AFTER COMING HOME FROM WORK? (Example, cough while sleeping)

    YES_____NO_____

13. IF YES, FOR HOW MANY HOURS?_____

    HOW MANY DAYS?_____

14. WHAT TIME OF DAY DO THEY STOP?_____

15. ARE THESE SYMPTOMS LESS SEVERE DURING WEEKENDS?

    YES_____NO_____

16. ARE THESE SYMPTOMS LESS SEVERE ON VACATION?

    YES_____NO_____

17. WHAT MONTH/YEAR DID THESE SYMPTOMS START?

    _____

17A. HOW MANY MONTHS WERE YOU ON THE JOB BEFORE SYMPTOMS STARTED?_____

18. IMPRESSION:

    (A) WORK RELATED SYMPTOMS PRESENT?

        YES_____NO_____

    (B) ARE SYMPTOMS ASSOCIATED WITH EXPOSURE TO A SUBSTANCE AT WORK?   YES_____NO_____

    (C) IF YES, WHAT PROCESS OR SUBSTANCE?

        _____

SMOKING HISTORY

19. DO YOU SMOKE CIGARETTES?

    NOW_____EX-SMOKER_____NEVER_____

20. HOW MANY PACKS PER DAY?_____

21.   HOW MANY YEARS HAVE YOU SMOKED?_____

NUMBER OF PACK YEARS:_____

CHRONIC BRONCHITIS

22.   DO YOU COUGH ON MOST DAYS FOR AT LEAST 3 MONTHS OUT OF THE YEAR?   YES_____NO_____

23.   IF YES, HOW MANY YEARS HAVE YOU HAD THIS COUGH?

_____

OTHER RESPIRATORY ILLNESS

24.   HAVE YOU EVER BEEN TOLD BY A PHYSICIAN THAT YOU HAVE EMPHYSEMA OR CHRONIC BRONCHITIS?

YES_____NO_____

ATOPIC HISTORY

25.   DO YOU HAVE ITCHY EYES, RUNNY AND CONGESTED NOSE DURING SPRING, SUMMER OR AUTUMN ON A YEARLY BASIS?

YES_____NO_____

26.   IF YES, WHAT YEAR DID THESE SYMPTOMS START?

_____

MDI OR TDI SPILLS IN PAST?

27.   IF SO, HOW MANY? (Interviewer: list dates and describe in detail)

_____

28.   SPILLS OR ACCIDENTAL EXPOSURE TO OTHER AGENTS AT WORK?

_____

_____

HOBBIES AT HOME

29. HAVE YOU EVER DONE SPRAY PAINTING AT HOME?

    YES_____NO_____

    IF YES, EXPLAIN_____

30. HAVE YOU EVER USED PLASTIC FOAM KITS AT HOME?

    YES_____NO_____

    IF YES, EXPLAIN_____

31. HAVE YOU PERSONALLY USED ADHESIVES, COATINGS OR POLYURETHANE VARNISHES AT HOME?

    YES_____NO_____

    IF YES, EXPLAIN

    _____

32. HAVE YOU EVER HAD RESPIRATORY SYMPTOMS WHILE USING THESE PRODUCTS AT HOME?

    YES_____NO_____

    IF YES, EXPLAIN_____

PHYSICIAN'S IMPRESSION–CIRCLE YOUR CHOICE

1. NO ASTHMA

2. NONOCCUPATIONAL ASTHMA

3. OCCUPATIONAL ASTHMA

4. BRONCHITIS

_____

PHYSICIAN'S SIGNATURE   DATE

Appendix 3

PEAK FLOW METER DIARY

NAME: _____ **DATE DISPENSED:** _____

INSTRUCTIONS:

1. Hold the peak flow meter level, be sure the air holes in back are not covered. Stand up. Take as deep a breath as possible. Put your mouth around the mouthpiece. Blow out as hard and as fast as you can. A short huff is okay. A long exhalation is not required.
2. Reset the arrow. Do the procedure three times and record all three readings.
3. Evening peak flows and morning peak flows should be done BEFORE taking any asthma medication. If an asthma inhaler has been used in the past two hours please note this on the diary.

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Work day? Y or N														
Hours worked														

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