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Measurement of human exposure to biologically relevant fractions of inhaled aerosols

John W Cherrie, Robert J Aitken

Abstract

Aerosol sampling has evolved with changes in technology and our understanding of the importance of assessing the biologically relevant fractions of the total aerosol. During the past decade there has been international agreement on the definitions for the inhalable, thoracic, and respirable fractions and instruments have been developed to collect samples according to these conventions. These measurement techniques are now well established in the workplace and are increasingly being applied to assessments of non-occupational exposure, as the practical difficulties in obtaining samples over 24 hours have been solved. It is argued that multiple aerosol size fractions should be measured for hazardous substances—such as inorganic lead—in which inhaled material may either be absorbed in the alveoli (respirable) or cleared from the ciliated airways in the lung to the gut and then absorbed (thoracic and extrathoracic). Such measurements should improve the evaluation of the risk for inhaled lead, particularly for non-occupational exposure of children. Also, passive aerosol sampling techniques may enable measurements of non-occupational exposure to be made over several weeks and this would also help improve the reliability of the risk evaluation for aerosol toxicants with a long biological half life. However, further development of these techniques is required if they are to be practicable and biologically relevant.

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It has long been recognised that the presence of particles in the air may adversely affect the health of exposed people. However, it is only in the past 100 years that serious attempts have been made to measure the size, shape, and concentration of airborne particles and to then relate these measures to human health. Inevitably, almost all of the early work was involved with measurement of aerosols in occupational settings such as mining, as it was in these situations that effects on health were most obvious.

Most of the early aerosol monitoring devices were designed to be placed in one place while the sample was collected. However, the advent of small and light battery operated pumps in the 1960s meant that personal exposure measurements became possible. Early personal samplers comprised simple open faced filter

holders that were thought to collect “total dust”. More complex devices, such as cyclones designed to collect only the finer fractions of airborne dust, became available only later. However, these improvements in technology enabled the links to be identified between occupational exposure to a range of aerosols and lung disease.

Developments in monitoring of exposure to aerosols have generally been focused towards sampling of occupational exposure, although the principles are equally applicable to non-occupational exposures. In the past, limitations on analytical sensitivity have dictated that environmental sampling of aerosols should be undertaken with high volume fixed location monitoring equipment. This is no longer the case and personal exposure measurements in non-occupational situations should help improve risk assessments.

In this paper we briefly review some of the recent developments in sampling methods used to assess human exposure to aerosols, and in particular, we look at issues of transferring experience from workplace sampling to non-occupational exposure monitoring. We use non-occupational exposure to inorganic lead aerosol as an example of the issues involved in developing an appropriate measurement strategy.

Early developments in aerosol sampling
Up to the mid-1920s the principal method of sampling aerosols was the sugar tube, later described by Walton.¹ This device comprised a 32 mm diameter tube filled to a depth of about 100 mm with 10–20 mesh sugar granules. Air was drawn through the granules by a hand operated pump and the collected dust was analysed by dissolving the sugar, and filtering the residue, which was then weighed to provide an estimate of the airborne mass. As well as being difficult to use, this method was criticised because reductions in the measured dust concentration in mines and other dusty environments were not matched by corresponding falls in dust related diseases.

More complex instruments soon became available. One such device was the konimeter, which was developed in 1916 by Kotze.² In this device, a small sample of air was drawn through a jet nozzle and directed towards a plate covered with petroleum jelly where the particles deposited by impaction. The plate was removed and the particles counted with a microscope. The operating principles of this device recognised that both the particle numbers and the particle size could be important determinants of risk. However, it was only able to collect a sample over a very short duration (about 1 second).

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By the mid-1930s there were several alternatives to the konimeter, the most important being the thermal precipitator.⁴ This overcame the limitations of the konimeter to collect very small particles ($<1\mu\text{m}$) and samples could be collected over much longer periods. The thermal precipitator had an inlet leading to a narrow channel where there was a heated wire oriented perpendicular to the direction of flow. As the contaminated air passed the wire, thermal gradients caused the particles to be deflected towards the walls of the sampler where two glass disks were located. After sampling, the glass disks were removed and the particles counted as with the konimeter. The thermal precipitator was a heavy bulky instrument that could only be used for fixed location measurements.

Partly because of ease and reliability of analysis, gravimetric sampling with filters to collect the dust from the air largely superseded particle counting methods. An early example of such an instrument is the Mine Research Establishment (MRE) type 113A gravimetric sampler⁴ which has been used in the mining industry in the United Kingdom to collect the British Medical Research Council (BMRC) respirable dust fraction.⁵ The respirable fraction was defined qualitatively as the fraction of the airborne dust that approximates to that which would reach and deposit in the alveoli, reflecting the belief that these particles were of greater importance in causing occupational lung disease, especially pneumoconiosis. With this device a close relation was established between the prevalence of pneumoconiosis and the mass concentration of respirable coal mine dust,⁶ whereas earlier attempts to correlate disease with the number of particles of dust had been less successful.⁷ The development of the BMRC respirable fraction was the first of what have become known as the "biologically relevant" aerosol size fractions that now form the basis of modern sampling methods.

Sampling of biologically relevant and other aerosol size fractions

Over the past 10 years substantial progress has been made towards standardising the sampling of aerosols to ensure that the fractions sampled are biologically relevant. In 1993 a new European standard for the definition of size fractions for measuring airborne particles was approved by the European Committee for Standardisation.⁸ This standard defines three sampling conventions: inhalable fraction (the mass fraction of airborne particles which is inhaled into the nose or mouth); thoracic fraction (the mass fraction of inhaled particles penetrating beyond the larynx) and respirable fraction (the mass fraction of inhaled particles penetrating to the unciliated airways). These three criteria are shown in figure 1. The same definitions, for workplace atmospheres, have also been adopted by the International Standards Organisation⁹ and The American Conference of Governmental Industrial Hygienists (ACGIH).¹⁰

These conventions recognise that only part of the total aerosol is inhaled into the nose or

mouth (the inhalable fraction). This concept was based on measurements of the aspiration efficiency of life sized human models reported by Ogden and his co-workers¹¹ and subsequently by Vincent and his colleagues.¹²⁻¹⁵ For large particles ($>50\mu\text{m}$, aerodynamic diameter) only about 50% of the total aerosol enters the respiratory tract according to the inhalable criteria, and this increases to almost 100% for small ($\sim 1\mu\text{m}$ diameter) particles. The thoracic and respirable conventions are subfractions of the inhalable aerosol and have their basis in a wide range of human volunteer deposition and clearance studies.¹⁶ However, the final forms of the definitions were a compromise in the case of the respirable convention between the BMRC curve and the previous ACGIH definition.¹⁷

The development of size conventions for measurement of ambient aerosol has been through a separate process to that of the workplace definitions and has been driven primarily by the deliberations of the United States Environmental Protection Agency. Greater emphasis in these considerations has been placed on the size distribution of aerosol in the ambient air but potential penetration into the human respiratory tract was also considered. The two commonly used environmental sampling conventions are PM_{10} and $\text{PM}_{2.5}$, both of which are curves falling from unity to zero with, in the case of PM_{10} , a 50% (0.5) value at $10\mu\text{m}$ and, for $\text{PM}_{2.5}$, a 0.5 value at $2.5\mu\text{m}$. Although not specifically designed to be so, the thoracic convention is almost identical to the PM_{10} size selection curve. There is, however, a significant difference between the respirable convention and the $\text{PM}_{2.5}$ curve.

It is now considered that personal samplers are much more effective tools for assessing exposure to aerosols in the workplace than static samplers. The types and performance of these devices have been described by other authors.¹⁸ In the main, these samplers have been targeted to meet either the inhalable convention—for example, the Institute of Occupational Medicine personal inhalable sampler¹⁹—or the respirable convention—for example, the Higgins cyclone.²⁰ As yet there are no commercial samplers for the thoracic convention although several research devices have or are being developed.²² The clear rationale is that sampling personal exposure provides a better evaluation of potential risks, as it has also been shown that personal

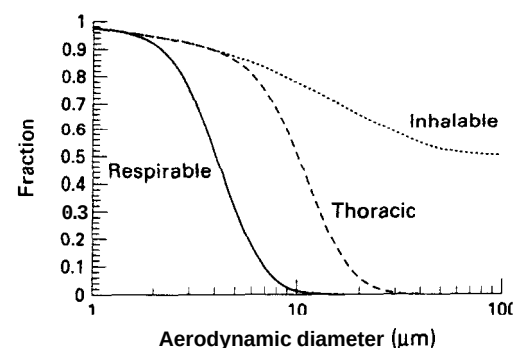


Figure 1 Inhalable, thoracic, and respirable sampling criteria.

exposures are almost invariably higher than those found with simultaneously operating fixed location monitors.²³

Measurement of exposure in non-occupational groups

Procedures for monitoring personal exposure to airborne particles in non-occupational situations have been adapted from those used in the workplace. The equipment generally comprises a small battery operated pump connected to a size selective sampling head containing a filter paper or some other particle collection system. The main problems associated with these techniques arise because of the low airborne mass concentrations in non-occupational situations and the necessity to sample over relatively long periods, typically 24 hours or more. As the person should wear the pump throughout the sampling period, except during sleep, it must be lightweight and quiet and this limits the maximum airflow. As a consequence, the minimum detectable mass concentration is generally about 10 µg/m³ over 24 hours.²⁴ The detection limit for components of the aerosol, such as lead, will be determined by the sensitivity of the analytical techniques used, but could be much less than for gravimetric assessments, perhaps about 10 ng/m³ for lead.²⁵

During personal sampling the entry into the sampling head is normally located close to the person's nose and mouth, typically on the outside of their clothing on a lapel to give an estimate of the concentration of particles inhaled. During the hours of sleep the sampler is generally placed in the individual's bedroom. To ensure that the noise of the sampler does not disturb the person during sleep some investigators have devised sound insulated boxes to muffle the pump noise.²⁴ These systems may also be used at other times when the noise would be distracting—for example, while watching television or reading. It is necessary to replace the pump battery about every 8 hours or to use mains electricity overnight.

There are several sampling heads that have been used to measure personal exposure to airborne particles. Measurements made more than 15 years ago may have been made as total suspended particulate (TSP), although this is a misnomer and these instruments generally had an undefined sampling characteristic which would have included some, but not all, of the larger particles suspended in the air. More recently measurements have been made with

the size selective sampling criteria described earlier. Even with such systems there is still the possibility that wearing a noisy pump may alter the person's behaviour and bias the measured exposure level.^{26, 27}

There are a few studies, mostly carried out over the past 10 years, which provide reliable measurements of personal exposure to airborne particles. These studies, which have been carried out in North America and more recently in Europe, do not generally measure the metal content of the aerosol. Most of the data refer to urban or suburban populations, generally excluding workers in occupations where there is known exposure to aerosols, and most measurements have been made over 24 hours. In total, there are about 2000 published measurements from various subgroups within society and only about 1200 measurements made in relation to currently accepted biologically relevant sampling conventions—such as thoracic aerosol (table).

In these studies the mean thoracic aerosol concentration ranged from 42 µg/m³ for the study of Seaton *et al.*²⁸ of elderly volunteers in Belfast to 105 µg/m³ for children in The Netherlands.²⁹ Most of these measurements were made over 24 hour periods and where this was not the case (Birmingham, UK) the data have been adjusted to estimate 24 hour exposure by using the average fixed point monitoring data to represent the unmeasured time. Other studies have shown that during the night indoor, outdoor, and personal concentrations agree quite well and so this adjustment seems justifiable.³⁰ The maximum individual thoracic concentration was 971 µg/m³ (24 hour average), measured by Loiy *et al.* in Phillipsburg, NJ.³¹

Sampling human exposure to lead aerosol

Sampling of lead aerosol in occupational situations is one of the few cases where current sampling practice does not require biologically relevant size selective sampling, although the method has been standardised. There is no agreement about how lead should be sampled outside the workplace.

There is also very little information about the size range of lead aerosols in ambient air in the United Kingdom. From the Quality of Urban Air Review Group (QUARG) report on airborne particulate matter in the United Kingdom³² about 90% of the lead aerosol is in the fine fraction (aerodynamic diameter <2.5

Measurements of thoracic aerosol exposure in various groups of non-occupationally exposed subjects over 24 hours

Study	Location	Study group	Subjects (n)	Measurements (n)	Geometric mean exposure (µg/m ³)	Maximum exposure (µg/m ³)
Loiy <i>et al.</i> ³¹	Phillipsburg, USA	Non-smoking volunteers	14	189	66	971
Pellizzari <i>et al.</i> ³⁰	Riverside, USA	Representative selection of non-smokers	178	171	98†	285†
Janssen <i>et al.</i> ²⁹	Amsterdam and Wageningen, Netherlands	Children aged 10–12 y	45	301	105‡	195
Mark <i>et al.</i> ³²	Central Birmingham, UK	Volunteers, smokers, and non-smokers	22	127	70§	260
Mark <i>et al.</i> ³²	East Birmingham, UK	Volunteers, smokers, and non-smokers	15	178	479	120
Janssen <i>et al.</i> ³³	Amsterdam, Netherlands	Non-smoking volunteers aged 50–70 y	37	262	59‡	113
Seaton <i>et al.</i> ²⁸	Edinburgh, UK	Volunteers aged >60 y	57	57	57	418
Seaton <i>et al.</i> ²⁸	Belfast, UK	Volunteers aged >60 y	52	54	42	288

†Population weighted median exposure rather than geometric mean.

‡Maximum is the estimated 98th percentile.

§Geometric mean estimated from arithmetic mean (SD).

§Estimated geometric mean and maximum, see text for explanation.

μm), probably associated with particles $<1\mu\text{m}$ in diameter.³³ It is possible that there may be greater concentrations of lead in the coarse fraction when lead contaminated dust, which is attached to other settled dust in the environment, is then resuspended. Because of the bonding of particles to surfaces, most dust which is resuspended will have a diameter $>1-5\mu\text{m}$.³⁴ Measurements of lead in household dust suggest that there may be substantial amounts of lead associated with larger particles.³⁵

When considering which size fraction or fractions are most appropriate for sampling human exposure to lead aerosol, we should consider the fate of the different size particles. Ideally, the measurement system should be capable of collecting the inhalable and respirable fractions. For lead particles which deposit in the alveolar region there is almost 100% absorption. However, only about 10% of the lead that is swallowed by adults is absorbed into the blood, although the proportion absorbed by children is higher, perhaps 30% to 40%.³⁶ The inhalable fraction less the respirable fraction represents that part of the aerosol which could potentially be absorbed through the gut and the respirable fraction that part which would be absorbed through the lung. These two measurements could then be combined as a weighted sum, based on the approximate efficiency of intake from each route of exposure. Alternatively, such data would provide reliable input data for developing the physiologically based pharmacokinetic models available for lead.³⁷

The United Kingdom Expert Panel on Air Quality Standards has recommended that there should be a standard of $0.25\mu\text{g}/\text{m}^3$ for lead, averaged over a year.³⁸ This standard is intended to protect the intellectual development of young people from inhaled lead aerosol. Unfortunately, the standard does not precisely specify the sampling procedure to be used and so it is unclear what size fraction it includes. For the fixed point measurements made by the United Kingdom Department of Environment, Transport, and the Regions this is probably unimportant because their samplers are generally located far from sources of coarse particles and most available samplers should give comparable results. However, differences in instrumentation would be much more important if the air quality standard were applied to personal exposure monitoring.

There is very little information on exposure to lead aerosol in the general population and the data that do exist have been obtained with samplers that do not conform to the agreed size selective sampling criteria.³⁹ Nevertheless, these data suggest that week long average lead exposures in Swedish adults range between 0.04 and $0.09\mu\text{g}/\text{m}^3$, as total dust. In the United Kingdom measurements of lead in the general atmosphere suggest that it makes up about 0.2% by mass of the thoracic (PM_{10}) aerosol. Applying this factor to the data shown in the table, assuming most of the variability in measured values is associated with the people

rather than the day of sampling, suggests that the average exposure level would be about $0.1\mu\text{g}/\text{m}^3$ and only about 5% of adults might exceed the United Kingdom air quality standard for lead. However, with the data from children there might be about half who could exceed the standard and it is this group who are especially at risk from lead exposure. Also, children living in homes where there was excessive lead contamination from flaking paint or from localised industrial sources might have personal exposures well above the standard.

Passive aerosol samplers

The appropriate averaging time for measurement should be dictated by the biological half life of the pollutant in the body with short term variations in exposure level being less relevant.³⁹ In the case of lead the biological half life is about 35 days³³ and this would be an appropriate averaging period. Clearly, measurement of personal lead exposure with conventional sampling strategies over such a long period is impracticable and the available data do not easily allow extrapolation to estimate such exposure. It might be possible to sample 24 hour average exposure on several occasions throughout a 5 week period and this would approximate to the long term exposure level, but this would still be costly and inconvenient for the subjects.

Sampling of gases and vapours has been revolutionised by the introduction of small lightweight samplers that do not have a pump but rely on the principle of diffusion to collect the material. Over the past 10 years there have been attempts to develop a similar approach for aerosols. The most promising of these, shown in figure 2, comprises a 25 mm diameter electret material held within an electrically conducting holder.⁴⁰ Electrets are polymers that have been treated to induce a permanent electrical charge within their structure, with the charge at the surface of the polymer as high as 1000 V. The sampler has a 1 cm gap between the surface of the electret and the front plate of the sampler and any particles that pass into this volume will drift towards the electret with a velocity proportional to their electrical mobility. The rate of collection of particles is relatively independent of their size, charge

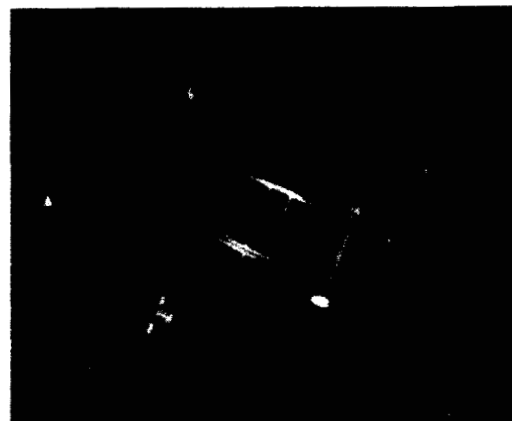


Figure 2 (A) Passive aerosol sampler developed by the United Kingdom Health and Safety Laboratory.

distribution, or velocity, but this is highly dependent on the electrical mobility and this depends on the chemical composition of the aerosol.⁴¹

The sampler is small, lightweight (about 15 g), and not intrusive. It may be worn for extended periods and requires almost no operator maintenance over that period. Therefore it would be an excellent device to assess aerosol exposure of non-occupational groups and could be used to measure exposure to lead, although there are several limitations that make its use problematic. The rate of collection by the device is very low. In a study which is currently underway to assess the use of the device in assessing urban domestic aerosols, collected masses over 2 week periods were of the order of 50 µg. Also, in its present form the sampler is not size selective. In principle at least, it collects all sizes with equal efficiency, although the range of sizes over which this holds has not been measured. Finally, as already described, the collection rate is dependent on the electrical mobility, and hence composition of the particles. It is therefore necessary to calibrate the collection rate for different types of aerosol by comparing the passive sampler with a conventional pumped sampler in each case. This may lead to the requirement for material specific designs, coupled with appropriate analytical methods to be produced. Further work is necessary if these limitations are to be overcome.

Conclusions

There have been many developments in the sampling of aerosols over the past decade. In this paper we have highlighted the important attempts to standardise the fraction of the aerosol that is sampled so that it roughly corresponds to the fraction penetrating to sections of the respiratory tract. There is now, for the first time, agreement between all those involved in sampling workplace aerosols to use the same definitions so that measurements of respirable aerosol made in the United States, Europe, and other parts of the world are comparable. It would be advantageous for those involved with sampling non-occupational aerosols to ensure that their measurements are obtained to the same standard.

A consequence of moving to biologically relevant size fractions is the desirability of obtaining measurements of multiple size fractions for some aerosols. We have used the example of lead, where measurement of the inhalable and respirable aerosol might be appropriate. Use of this type of approach would certainly allow a more precise estimate of the biologically relevant exposure to be made and would enable more accurate estimates of risk from inhaled aerosol. It is more important to select an appropriate sampling system for personal exposure measurements than for fixed point monitoring because of the likelihood of resuspended dust playing a greater part and this should be carefully considered when sampling aerosols outside the workplace.

Finally, selecting an appropriate averaging time provides a particular challenge for all hazardous aerosols that have a chronic effect on health. Here there is an advantage in having sample averaging times as long as possible, consistent with the biological half life of the pollutant, so as to reduce the variability associated with short term samples. Continuous personal sampling for aerosols over several days or weeks is currently impracticable, but further development of passive samplers offers the possibility of adopting such strategies in the future. The key difficulty will be to develop systems which combine the need to obtain size selective samples with that of measuring over prolonged periods.

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Occup Environ Med, together with many other international biomedical journals, has agreed to accept articles prepared in accordance with the Vancouver style. The style (described in full in the *JAMA* [1]) is intended to standardise requirements for authors, and is the same as in this issue.

References should be numbered consecutively in the order in which they are first mentioned in the text by Arabic numerals on the line in square brackets on each occasion the reference is cited (Manson [1] confirmed other reports [2] [3] [4] [5]). In future references to papers submitted to *Occup Environ Med* should include: the names of all

authors if there are three or less or, if there are more, the first three followed by *et al*; the title of journal articles or book chapters; the titles of journals abbreviated according to the style of *Index Medicus*; and the first and final page numbers of the article or chapter. Titles not in *Index Medicus* should be given in full.

Examples of common forms of references are:

- 1 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *JAMA* 1993;269:2282-6.
- 2 Soter NA, Wasserman SL, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- 3 Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology, mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.

Conceptual model for assessment of dermal exposure

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Abstract

Dermal exposure, primarily to pesticides, has been measured for almost **half** a century. Compared with exposure by inhalation, limited progress has been made towards standardisation of methods of measurement and development **of** biologically relevant exposure measures. It is suggested that the absence **of** a consistent terminology and a theoretical model has been an important cause **of** this lack of progress. Therefore, a consistent terminology based **on** a multicompartment model for assessment of dermal exposure is proposed that describes the transport of contaminant **mass** from the source of the hazardous substance to the surface of the **skin**. **Six** compartments and two barriers together with eight **mass** transport processes are described. With the model structure, examples are given of what some existing methods actually measure and where there are limited, or **no**, methods for measuring the relevant mass in a compartment or transport of **mass**. The importance of **measuring** the concentration of **contaminant** and not mass per area in the **skin** contaminant layer is stressed, as it **is** the concentration difference between the **skin** contamination layer and the perfused tissue that drives uptake. Methods for measuring uptake are currently not available. Measurement of **mass**, concentration, and the transport processes must **be** based **on** a theoretical model. Standardisation **of** methods **of** measurement **of** dermal exposure is strongly recommended.

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Keywords: dermal **exposure**; model; measurement methods

Exposure to hazardous substances most commonly occurs either by inhalation, ingestion, dermal contact, or some combination of these routes. Occupational hygiene has traditionally focused on exposure by inhalation because it was almost invariably considered to be the most important pathway. Many methods have been developed to measure exposure levels from inhalation and there is a clear understanding of how such levels should be interpreted to help reduce risk. The situation is less clear for the dermal route of exposure. Practical methods of measurement have been developed to assess dermal exposure' and proposals have been made to develop dermal

exposure limits in an analogous way to those for inhalational exposure.^{1,2} However, there has been criticism of the existing methods of measurement of dermal exposure because they determine the mass of contaminant either depositing on the **skin** or retained **on** the **skin** at the end of the exposure period.^{3,4}

Hazardous substances on the dermal surface will be taken up continuously into the body through the stratum corneum and the epidermis towards the dermis where they or their dermal metabolites will be removed by the blood flow. The transport process is driven by the concentration gradient between the dermal surface and the perfused tissue. The risk arising from dermal exposure is thus firstly related to the time dependent concentration of a substance on the dermal surface rather than the mass of material on that surface at any given time. Mass is nevertheless important when there is little material available for uptake.

Contamination of the skin may arise in many different ways. It is possible for hazardous substances to land on or be absorbed into the skin directly from the air. They may be transferred to the **skin** from contact with contaminated surfaces or by submersion of part of the body into the substance. **Also**, the contaminant may be lost from the skin, either by evaporation or some other mechanisms such as washing or abrasion, without being taken up into the body. Finally, the presence of clothing or protective garments may **modify** the rate at which hazardous substances come into contact with the **skin**. All of these processes are important to consider when **making** an assessment of dermal exposure and a complete understanding of these complex processes will help in developing an appropriate control strategy.

In this paper we have attempted to produce a consistent terminology for assessment of dermal exposure. The terminology is based on a conceptual model of the processes leading to exposure (from the source of a hazardous substance to the surface of the **skin**). We have also defined several terms related to exposure, which provide a valid basis for investigating the risks posed by dermal exposure. It has not been our intention to consider the process of uptake into the body or the derivation of dose estimates from dermal exposure, although others have developed models that could be used in such **contexts**.^{5,6}

Conceptual model of dermal exposure
A consistent terminology has to be based on a coherent and systematic description of dermal exposure scenarios. A multicompartment

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model is an appropriate basis for a terminology as it comprises distinct physical objects or compartments connected by mass transport processes. Models of this type are concerned with what happens—for example, where fingers get contaminated by touching a surface—and not why it happens—for example, particle adhesion.

COMPARTMENTS

All compartments are assumed to be well and instantaneously mixed. As a result the concentration in a compartment is described by the amount of mass and distribution volume of the

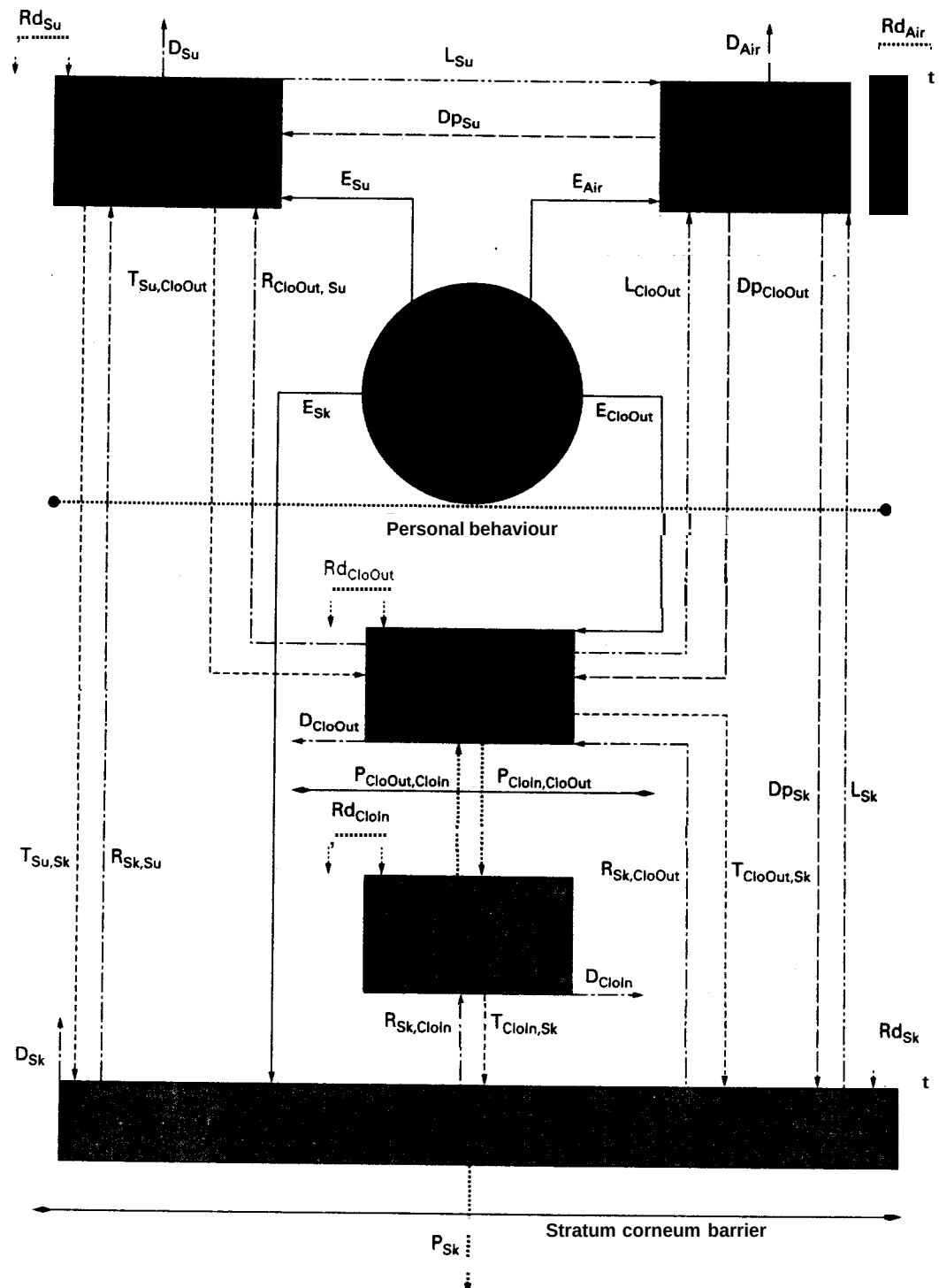
compartment. Six principle compartments are being distinguished in the model (figure):

Source (S)

Processes or activities, from which a mass is being introduced into any of the compartments, will be considered as sources.

Air

The air compartment contains vapours and dispersed particles, which are assumed to be homogeneously distributed in the compartment. The total mass of a given substance in the air compartment is well defined and can, in



Overview of the conceptual model, compartments and rate constants. E =emission (—); Dp =deposition (—); L =resuspension or evaporation (—); T =transfer (—); R =removal (—); Rd =redistribution (—); D =decontamination (—); P =permeation and absorption (—).

principle, be measured. The compartment volume is given by the size of room or other boundaries, either physical or virtual.

Surface contaminant layer (*Su*)

Contaminants on a surface form a layer, which delineates the compartment called the surface contaminant layer. The compartment is assumed to be homogeneous. In principle, all substances belonging to the surface contaminant layer can be identified and thus mass in this compartment can be assessed. The compartment volume is given by the three dimensional volume of this layer. For many practical purposes, a two dimensional representation of this layer will suffice.

Outer and inner clothing contaminant layer (*CloOut*, *CloIn*)

Solid or liquid contaminants at the boundary between outside and the surface of the outer clothing are modelled as the compartment called outer contaminant layer. The fabric separates this compartment from the inner clothing contaminant layer. For simplicity of the model the fabric is described as a barrier (mass transfer rate limiting) having the property to retain mass ($M_{\text{Reservoir}}$). If the mass of the hazardous substance in the outer clothing contaminant layer compartment is M_{CloOut} then some of this material will be transported through the clothing to the compartment called inner clothing contaminant layer. The mass in the inner clothing compartment is $M_{\text{CloIn}} = M_{\text{CloOut}} - M_{\text{Reservoir}}$. For many practical purposes a two dimensional representation of these compartments will suffice.

Skin contaminant layer (*Sk*)

On the **skin**, contaminants, sweat, **skin** oil, and barrier cream (if applied) form a layer. This layer constitutes the **skin** contaminant layer. The compartment is assumed to be homogeneous. In principle, all substances belonging to the **skin** contaminant layer can be identified and thus the mass in this compartment can be identified and measured. The compartment

volume is given by the three dimensional volume of this layer. The conventional two dimensional representation of this layer is an oversimplification, which has contributed to the confusion about the principles involved in the choice of measurement and interpretation of dermal contamination in terms of dermal uptake.

MASS TRANSPORT PROCESSES

The mass transport from the source to the compartments and sinks in the system is shown in the figure. Below the horizontal dotted line in the figure a person's movement begins to influence the transport processes. **Two** units are used to measure transport of mass; g.s^{-1} and g.event^{-1} . For processes called events, it is important to describe the number of events within a reference period, typically 8 hours. The mass transport can be divided into eight distinct processes as described later and in table 1.

Emission (E)—Emission (E) is the transport of substances into the air, onto surfaces, outer clothing, and the **skin** contaminant layer from all primary sources. Evaporation of liquids or emission of droplets or particles into the air gives rise to emission of contaminant mass to the air. For aerosols we restrict this emission pathway to those with aerodynamic diameter $<100 \mu\text{m}$ so that sedimentation is relatively unimportant. Emission to the different surfaces in the model can arise from splashing, spilling, immersion, and impaction of large particles. Splashing is the emission of large droplets the trajectory of which towards the surfaces is unaffected by air movement, whereas spilling is the event by which a liquid or powder is spilled on a surface. Immersion is an event whereby a part of the body is submerged into a liquid or a powder. Impaction is the process by which large particles are generated at the source and ejected from that source to impact onto surfaces. The emission rate is given as either g.s^{-1} or as g.event^{-1} .

Deposition (Dp)—Deposition (Dp) is the transport of substances from the air to surfaces,

Table 1 Compartment descriptors

Compartment	Definition of metric	Symbol	Relation	Units
Source	Mass of hazardous substance available for emission Concentration of a hazardous substance in the source	M_s C_s		g $\text{g.g}^{-1}, \text{g.m}^{-3}$
Air	Mass of substance in the air compartment Volume of the air compartment	M_{Air} V_{Air}		g m^3
Surface contaminant layer	Concentration of hazardous substance in the air Mass of a hazardous substance in the surface contaminant layer Concentration of a hazardous substance on the surface Area of surface which is contaminated with hazardous substance	C_{Air} M_{Su} C_{Su} A_{Su}	$M_{\text{Su}}/(M_{\text{Su}} + M_{\text{Other}})$	g/m^3 g g.kg^{-1} cm^2
Outer clothing Contaminant layer	Mass of hazardous substance in the outer clothing contaminant layer compartment Concentration of a hazardous substance in the outer clothing compartment Area of the outer clothing which is contaminated with hazardous substance	M_{CloOut} C_{CloOut} A_{CloOut}	$M_{\text{CloOut}}/(M_{\text{CloOut}} + M_{\text{OtherOut}})$	g g.kg^{-1} cm^2
Inner clothing contaminant layer	Mass of hazardous substance in the inner clothing contaminant layer compartment Concentration of a hazardous substance in the inner clothing compartment Area of the inner clothing which is contaminated with hazardous substance	M_{CloIn} C_{CloIn} A_{CloIn}	$M_{\text{CloIn}}/(M_{\text{CloIn}} + M_{\text{OtherIn}})$	g g.kg^{-1} cm^2
Skin contaminant layer	Mass of hazardous substance on the skin surface Concentration of hazardous substance in the skin contaminant layer Area of the skin which is contaminated with hazardous substance	M_{Sk} C_{Sk} A_{Sk}	$M_{\text{Sk}}/(M_{\text{Sk}} + M_{\text{Other}})$	g g.kg^{-1} cm^2

M_{Other} = mass of all other substances in a particular compartment.

outer clothing, and the skin contaminant layer. Deposition can be of mass as either solid, liquid, or vapour. The time dependent mass deposition rate $Dp(t)$, in units of g.s^{-1} , can be represented by the deposition velocity $v(t)$ in units of cm.s^{-1} as follows:

$$Dp(t) = v(t) \cdot C(t) \cdot A, \quad (1)$$

where $C(t)$ is concentration in air outside the boundary layer and A is the area of the two dimensional representation of the compartment, where X is either **Su** for surface, C_{lo} for clothing, or S_k for skin).

Resuspension or evaporation (L)—Resuspension or evaporation (L) is the transport of substances from surfaces, outer clothing, and the skin contaminant layer to the air, as particulate (resuspension), vapours, or both. Evaporation is a continuous process driven by diffusion. Mechanical forces cause resuspension. If resuspension is caused by a single mechanical impact then the transport of mass is conveniently modelled as a transfer of mass per single event. If resuspension is caused by a sudden flow of air along a surface, there is a short initial peak of resuspended mass followed by a decay of resuspended mass per time. Thus resuspension can, in general, be measured as a transport of mass per single event.

Transfer (T)—Transfer (T) is the transport of substances by direct contact between surface, skin, and outer and inner clothing Contaminant layers in a direction towards the worker. Transfer from the surface to the skin contaminant layer is event based and takes place from a small area of actual contact. That area could be considerably smaller than the surface area of the body part involved in the contact. The actual surface area of the skin that will be contaminated, as well as the efficiency of mass transfer, will depend on the actual contact—for example, single pressure, or movements of the skin along the surface.

Removal (R)—Removal (R) is the transport of substances by direct contact between skin, inner and outer clothing, and surface contaminant layer in a direction away from a worker. Removal thus is defined as an event based transport in the opposite direction of transfer.

Redistribution (Rd)—If contaminants in the air, on the surface, clothing, or skin are not homogeneously distributed, or different parts of the body such as palm, neck, and trunk need to be distinguished, the compartments can be subdivided initially into subcompartments. Redistribution then is the transport of substances from a subcompartment to another subcompartment of the same type. Redistribution of contaminants from one part of the skin contaminant layer to another can occur as a result of touching the face with contaminated fingers. Also, fabric wetting can redistribute liquid contaminants.

Decontamination (D)—Decontamination (D) is the deliberate transport of contamination from the system—for example, ventilation of room air, cleaning of room surfaces and outer clothing, or washing material off the skin. The air compartment is decontaminated by the combined effect of natural and mechanical ventilation. Cleaning of contaminated surfaces, chang-

ing of clothing, and cleaning of skin all result in permanent loss of mass from the system and thus are decontamination processes. By contrast, brushing dust off clothing transports particulate mass to the room air and thus is resuspension, not decontamination.

Penetration and permeation (P)—Penetration and permeation (P) both involve transport of substances through a rate limiting barrier—such as clothing or the stratum corneum. Penetration is transport caused by external pressure, capillary penetration, and evaporation-condensation. Permeation always involves diffusion.

Transport of contaminants through permeable clothing occurs by aerosol penetration and liquid transport. External air pressure can be considered to be the driving force for penetration of aerosols through fabric,⁸ whereas the mechanisms of liquid transport are capillary penetration, pressure penetration, impact penetration, and evaporation-condensation? Mass transport through non-permeable clothing is a diffusion process driven by concentration.

The rate of mass transport through the stratum corneum $P_{sk}(t)$ can be represented by a permeability coefficient $K(t)$, the concentration difference over the stratum corneum $C_{sk}(t)$, and skin contaminant layer area $A(t)$ as:

$$P_{sk}(t) = K(t) \cdot C_{sk}(t) \cdot A(t) \quad (2)$$

The area of the skin contaminant layer can be time dependent, which for example is the case for a drop that dries while on the skin. Roed *et al*¹⁰ have shown that very small particles may penetrate into the stratum corneum but their fate is not known.

Concentration

The model describes transport of mass of a given substance, which is a conserved quantity provided we neglect chemical reactions. However, several transport processes are driven by the compartment concentration. For the air compartment concentration is readily obtained from mass because an air compartment can be defined so that it has a constant volume. For the surface and skin contaminant layers, volume is defined by the total amount of material present (table 2). If the skin contaminant layer compartment only contains liquids the concentration C_{sk} of a hazardous substance of mass M_{sk} is given by the ratio

$$C_{sk} = M_{sk} / (M_{sk} + M_{sk,other}) \quad (3)$$

where $M_{sk,other}$ is the mass of all other liquid substances. This concentration can be readily transformed into the molar concentration, which is more relevant for the skin contaminant layer. As a first approximation and for substances of low volatility C_{sk} can be considered to be the concentration in the bulk liquid.

The concept of concentration is more complicated for particles as they are discrete entities and solid substances must dissolve to diffuse through the stratum corneum. For soluble or leachable substances it is the concentration in the wet layer around the individual particle that has to be used for C_{sk} in equation 2. This may mean that uptake will be limited by the rate of dissolution rather than diffusion through the stratum corneum. Fur-

Table 2 Mass transport process descriptions

Process	Definition	Symbol	Units
Emission	Mass of hazardous substance emitted into air from primary sources per unit time	E_{Air}	$g.s^{-1}$
	Mass of hazardous substance emitted to surface contaminant layer by splashing, spilling and ejection of particles from primary sources per unit time per event	E_{Su}	$g.s^{-1}$ $g.event^{-1}$
	Mass of hazardous substance emitted to the outer clothing contaminant layer for a particular worker by splashing, spilling and ejection of particles from primary sources per unit time per event	E_{CloOut}	$g.s^{-1}$ $g.event^{-1}$
	Mass of hazardous substance emitted to skin contaminant layer for a particular worker by splashing, spilling and ejection of particles from primary sources per unit time per event	E_{Sk}	$g.s^{-1}$ $g.event^{-1}$
Deposition	Mass of hazardous substance deposited from air compartment to the surfaces per unit time	$D_{P_{Su}}$	$g.s^{-1}$
	Mass of hazardous substance deposited from the air compartment to the outer clothing contaminant layer for a particular worker per unit time	$D_{P_{CloOut}}$	$g.s^{-1}$
	Mass of hazardous substance deposited from the air compartment to the skin contaminant layer for a particular worker per unit time	$D_{P_{Sk}}$	$g.s^{-1}$
	Mass of hazardous substance lost from the surface contaminant layer to the air compartment by evaporation per unit time or by resuspension or evaporation per event	L_{Su}	$g.s^{-1}$ $g.event^{-1}$
Resuspension or evaporation	Mass of hazardous substance lost from the outer clothing contaminant layer of a particular worker to the air compartment by evaporation per unit time or by resuspension or evaporation per event	L_{CloOut}	$g.s^{-1}$ $g.event^{-1}$
	Mass of hazardous substance lost from the skin contaminant layer of a particular worker to the air compartment by evaporation per unit time or by resuspension or evaporation per event	L_{Sk}	$g.s^{-1}$ $g.event^{-1}$
	Mass of hazardous substance untransferred from the surface contaminant layer to the skin contaminant layer for a particular worker by direct contact per event	$T_{Su,Sk}$	$g.event^{-1}$
	Mass of hazardous substance transferred from the surface contaminant layer to the outer clothing contaminant layer for a particular worker by direct contact per event	$T_{Su,CloOut}$	$g.event^{-1}$
Transfer	Mass of hazardous substance untransferred from the inner clothing contaminant layer to the skin contaminant layer for a particular worker by direct contact per event	$T_{CloIn,Sk}$	$g.event^{-1}$
	Mass of hazardous substance transferred from the outer clothing contaminant layer to the skin contaminant layer for a particular worker by direct contact per event	$T_{CloOut,Sk}$	$g.event^{-1}$
	Mass of hazardous substance removed from the skin contaminant layer of a particular worker and untransferred to the surface contaminant layer by direct contact per event	$R_{Sk,Su}$	$g.event^{-1}$
	Mass of hazardous substance removed from the skin contaminant layer and transferred to the inner clothing contaminant layer of a particular worker by direct contact per event	$R_{Sk,CloIn}$	$g.event^{-1}$
Removal	Mass of hazardous substance removed from the skin contaminant layer and transferred to the outer clothing contaminant layer of a particular worker by direct contact per event	$R_{Sk,CloOut}$	$g.event^{-1}$
	Mass of hazardous substance removed from the outer clothing contaminant layer of a particular worker and transferred to the surface contaminant layer by direct contact per event	$R_{CloOut,Su}$	$g.event^{-1}$
	Mass of hazardous substance transferred from one pan of air compartment to other part per event	Rd_{Air}	$g.event^{-1}$
	Mass of hazardous substance transferred from one part of contaminant layer to other pan per event	Rd_{Su}	$g.event^{-1}$
Redistribution	Mass of hazardous substance transferred from one part of inner clothing contaminant layer to other part per event	Rd_{CloIn}	$g.event^{-1}$
	Mass of hazardous substance transferred from one pan of outer clothing contaminant layer to other part per event	Rd_{CloOut}	$g.event^{-1}$
	Mass of hazardous substance transferred from one part of skin contaminant layer to other pan per event	Rd_{Sk}	$g.event^{-1}$
	Mass of hazardous substance removed from the air compartment by ventilation per unit of time	D_{Air}	$g.s^{-1}$
Decontamination	Mass of hazardous substance removed from the surface contaminant layer by deliberate decontamination per event	D_{Su}	$g.event^{-1}$
	Mass of hazardous substance removed from the outer clothing contaminant layer by deliberate decontamination per event	D_{CloOut}	$g.event^{-1}$
	Mass of hazardous substance removed from the inner clothing contaminant layer by deliberate decontamination per event	D_{CloIn}	$g.event^{-1}$
	Mass of hazardous substance removed from the skin contaminant layer by deliberate decontamination per event	D_{Sk}	$g.event^{-1}$
Penetration and permeation	Mass of hazardous substance transported through stratum corneum	P_{Sk}	$g.s^{-1}$
	Mass of hazardous substance transported from the outer clothing contaminant layer to the inner clothing contaminant layer per unit time	$P_{CloIn,CloOut}$	$g.s^{-1}$
	Mass of hazardous substance transported from the inner clothing contaminant layer to the outer clothing contaminant layer per unit time	$P_{CloOut,CloIn}$	$g.s^{-1}$

Air=air compartment; **Su**=surface contaminant layer; **Sk**=skin contaminant layer; **CloOut**=outer clothing contaminant layer; **CloIn**=inner clothing contaminant layer.

thermore, if uniform deposition takes place a monolayer of particles may be built up until the entire surface is covered. As a multilayer forms, the additional mass will have less and less influence on uptake and may be likely to dislodge and fall off. For this reason the mass of particles in the **skin** contaminant layer may only have limited relevance to uptake.

Measurement methods of skin and surface contamination

Depending on the perspective from which the exposure scenario is investigated a range of measurement approaches have been developed from the 1950s onwards." Table 3 lists methods in common use for **skin** and surface contamination. Several of these methods are used to assess both compartment mass—for example, total mass in surface layer—and mass transport processes—for example, dislodgeable mass. A clear distinction is not always made and this can create confusion about determination and interpretation of sampling efficiencies. As an example, measurement methods should aim to have 100% sampling efficiency where they intend to assess compartment mass. On the other hand, a 100% sampling efficiency for a wipe test to measure the transfer to **skin** upon

contact with a surface is not necessarily desirable.' The amount that can be transported from surfaces to the **skin** or outer clothing contaminant compartments depends on the type of surface, the contaminant, and on the forces acting on the contaminant layer, rather than how much mass is present in the compartment. Measurement of transport must therefore be based on a model. Several routes may be followed. The transport process from surfaces could be simulated with, for example, a standardised instrumental sampling method or standardised events. Transport can also be measured during actual field conditions for an exposed population, with the result summarised in the form of a distribution of mass transport. Such reported distributions have been used for risk assessment—for example, transfer from soil giving the results as soil to **skin** adherence."

Deposition from air is more predictable and Schneider and Stokholm³³ have proposed a theoretical model dependent on particle size for the transport of airborne dust onto the ocular surface, in relative deposition velocities. This could be called the ocular deposition fraction, by analogy with the inhalable fraction. Roed et al¹⁰ have given experimental data for

Table 3 Measurement methods (for a review see Carson et al¹¹)

Method	Principle of sampling	Sampling area definition	Measured compartment mass*	Measured transport process†	Reference
UV Fluorescence	In situ	0.1–2 m ²	$M_{Sk}, M_{Su}, M_{CloOut}$	All processes	13–17
Portable x ray fluorescence monitor	In situ	Instrument defined	M_{Su}	All processes related to the surface contaminant layer	18
Wet wipe	Manual wiping	None or template	M_{Su}, M_{Sk}	$T_{Su,Sk}, T_{Su,CloOut}, R_{Sk,Su}, R_{Sk,CloIn}$	19
Wet wipe	Mechanised wiping	Instrument defined	M_{Su}	$R_{Sk,CloOut}$	20
Gelatine foil	Surface dust lifting	1:1 transfer of dust layer	M_{Su}	$T_{Su,Sk}, T_{Su,CloOut}$	21
Fixed pressure dislodgeable residue sampler	Mechanical transfer in situ	10–20 cm x length sampled	M_{Su}	$T_{Su,Sk}, T_{Su,CloOut}$	22
Dislodgeable foliar residue sampling	Surface removal	Punches 0.1–2.5 cm ² , total 100 cm ²	M_{Su}	$T_{Su,Sk}, T_{Su,CloOut}$	23
Adhesive tape	Skin stripping	1:1 transfer of dust layer	M_{Sk}	$DP_{Sk}, R_{Sk,Su}, R_{Sk,CloIn}, R_{Sk,CloOut}$	24
Hand wash	Wash with water or alcohol	Total hand surface	M_{Sk}	$R_{Sk,Su}, R_{Sk,CloIn}, R_{Sk,CloOut}, D_{Sk}$	25
Patch	Passive	Sampler defined	M_{Sk}	$T_{Su,Sk}, T_{CloIn,Sk}, T_{CloOut,Sk}, DP_{Sk}$	26
Whole body	Passive	Body parts	M_{Sk}	$T_{Su,Sk}, T_{CloIn,Sk}, T_{CloOut,Sk}, DP_{Sk}$	26
SMAIR	Resuspension by air jet	Instrument defined	—	L_{Su}	27
STEPP	Resuspension by impact	Instrument defined	—	L_{Su}	28
Microvacuuming	Resuspension by suction	Instrument defined	M_{Su}	L_{Su}	29
FLEC	Evaporation by airflow	Instrument defined	—	L_{Su}	30
TEWL	Evaporation	Instrument defined	—	L_{Sk}	31

*Definition of symbols as for table 1.

†Mass transport process descriptions as for table 2.

mean deposition velocities on arms and other body parts for people seated in a test room, which likewise could form a basis for defining other dermal deposition fractions.

There is a close analogy to requirements for sampling inhalable airborne particles. Historically, fractions with biologically relevant particle size have been based on experimental data that reflect mean deposition efficiencies in the airways. An alternative approach has been to define the fraction as that obtained by a given sampling instrument. Initially there were different proposals for the size fractions, and samplers were not available which could measure according to these criteria. However, better experimental data on deposition efficiencies has resulted in the adoption of an international standard for the definition of the respirable, thoracic, and inhalable fractions.³⁴ Recent development has resulted in samplers, which have aspiration efficiencies that match the definition of the fractions.³⁵

In the following section some strategies for measuring with the model compartment mass and mass transport processes will be discussed, highlighting several problems in conventional approaches to measurement and possible routes forward.

COMPARTMENTS

The mass in a compartment at a given time can in principle be measured by sampling all of the contaminant present at that time in the compartment. A strategy often used in monitoring is to estimate the entire compartment mass by sampling a small proportion of the whole.^{26,36}

Air

Methods for measurement of concentration of hazardous substances in the air compartment are well established relative to estimation of inhalation risk. For aerosols specifications are available for sampling fractions of biologically relevant inhalable size,³⁴ but methods for measuring the concentration of non-inhalable particles, which are relevant for estimating surface deposition, have not yet been developed.

Surface contaminant layer

For surfaces, several in situ methods are available, but they can **only** measure a limited **range** of substances, and never total mass. Portable x ray fluorescence analysis is one example of this type of analysis.¹⁸ Methods based on removal—such as adhesive tape sampling—can have a **high** sampling efficiency. The efficiency in field use is **usually** estimated with consecutive sampling **of** the same area. However, **this** is based on a circular argument, as only the contaminant that the tape can actually remove will ever be sampled.¹⁹

Clothing contaminant layers

In the model clothing was divided into an outer and inner contaminant layer, with a buffer to represent the mass residing inside the clothing which does not come into contact with surfaces or skin, respectively. Measurement of the entire mass in the clothing would in principle be no problem **and** if this were done for non-permeable fabrics theoretically the outer contaminant layer would be measured. To our knowledge a method which measures the inner contaminant layer for permeable layers is not available.

Skin contaminant layer

The skin rinse method²⁵ has been used to assess the mass in the skin contaminant layer compartment. The method typically recovers 40%–90% **of** contaminants spiked onto the skin. Recoveries can be measured experimentally. However, spiking experiments have inherent problems as it is unclear whether **this** result should be interpreted as a 40%–90% sampling efficiency for the skin contaminant layer or if it reflects partitioning between this compartment and the stratum corneum or perfused tissue.

Measurement methods based on UV fluorescence of tracer compounds mixed with the contaminant at source^{13–17} indirectly measure the mass of the contaminant in the skin contaminant layer. However, fluorescent tracers have the ability to bind with the cell proteins in the stratum corneum and the method is not able to dif-

ferentiate between the **skin** contaminant layer and the stratum corneum.

MASS TRANSPORT PROCESSES

Transport can in principle be measured with a mass balance calculation for the change in mass in all relevant compartments per event or per time. Transport can more directly be determined by methods which standardise a set of external factors that are considered to be important determinants of the transport process (table 3).

Deposition

Adhesive tape can measure the particle deposition unaffected by loss. This has been done for particle deposition onto the face," but the method does not work for parts of the body that get into contact with other surfaces. Charcoal cloth has been used to measure **skin** deposition of volatile compounds. A problem is that the method does not differentiate between vapours from air and liquid **splashes**.^{38, 39}

Resuspension or evaporation

Resuspension is usually best described as a series of single events. If events are repeated, say at frequency γ , and the ratio γ/T tends to infinity, where T is a suitable reference time interval, resuspension can be treated as a continuous process. In this case it is customary to define a resuspension rate R by the equation where the mass of substance lost from the surface per unit time $\mathcal{E}$ (table 2) is:

$$L(g\ s^{-1}) = R(s^{-1}) \cdot M_{sk}(g) \quad (4)$$

This definition assumes that R is independent of M_{sk} (see also discussion for transfer).

An approach to assess resuspension based on events would be to collect all dust resuspended as the result of a standardised mechanical impact. Kildesø *et al*²⁸ have developed the surface total emission potential of particles (STEPP) tester, which simulates resuspension caused by a walking person from a carpet. Resuspension caused by air movements is simulated in the SMAIR tester." In this instrument a well defined air jet is directed at a surface contaminant layer and the resuspended particles collected on a filter. Vacuuming techniques could be used to simulate resuspension caused by strong air velocities, provided the nozzle does not touch the surface.

Evaporation is driven by diffusion and thus it is simpler to specify external factors. Wolkoff³⁰ has developed a field and laboratory emission cell (**FLEC**), which in principle is a small air compartment that is placed on a surface. A well defined flow of conditioned air is passed through the compartment and the exhaust air is analysed for evaporated substances. The diffusive transport of water vapour from the **skin** (transepidermal water loss) can be measured simply with instruments.³¹ A similar principle could be used for other vapours lost from the skin.

Transfer

The increase in mass over time in the **skin** contaminant layer is the measured net balance between transport to and from the compartment and thus is affected by deposition, resuspension

or evaporation, removal, and uptake. Surrogate **skin** methods such as pads, gloves, and coveralls are based on the assumption that they are estimates of the transport of mass to the **skin** contaminant layer from surfaces. However, the materials used do not have the roughness, stickiness, and other properties of human **skin** and so may not meet this assumption.

Dislodgeable foliar residue, a procedure first described by Iwata *et al*,²³ determines the pesticide remaining on foliage after spraying. It involves destructive sampling of foliage by punching or removing leaves to provide a sample leaf area of about 100 cm² and subsequent, partly mechanical partly chemical, removal of pesticide residue by shaking the leaves in water with some drops of surfactant. This process is intended to mimic transfer to **skin**. Then pesticide is extracted from the water and analysed chemically. Sometimes an organic solvent is used in the first step, but this then measures the mass in the compartment rather than the dislodgeable foliar residue. Both methods, however, have been used to indicate the strength to transfer by direct contact from the source, which may be relevant to predict exposure by contact. A more general form of dislodgeable foliar residue is transferable residue (TR). If TR is measured simultaneously with an increase per event of mass per area M_{sk}/A_{sk} in the **skin** contamination layer, a dermal transfer coefficient (DTC) can be defined as:⁴⁰

$$DTC\ (cm^2 \cdot event^{-1}) = M_{sk}(g \cdot event^{-1}) / A_{sk} TR(g \cdot cm^{-2}) \quad (5)$$

For this equation to be useful it has to be assumed that TR is independent of M_{sk}/A_{sk} . However, Brouwer *et al*⁴¹ have shown that TR depends non-linearly on the mass per area in the surface contaminant layer, M_{su}/A_{su} . A better approximation would be to assume a functional relation:

$$TR = TR(M_{su}/A_{su}) \quad (6)$$

determined by non-linear regression. In reality a stochastic relation must be expected, and thus for given M_{su}/A_{su} , TR has a given distribution with variables (mean and variance) being functions of M_{su}/A_{su} . It is to be expected that liquid contaminants can be assessed with the simple relation, grease or other paste-like contaminants an intermediate relation, and particulate contaminants with the most complex relation. Transfer of particles will depend on contaminant properties—such as particle size, distribution, shape, and humidity or cohesion. In all cases it must be remembered that TR will depend on the method used for its measurement.

There are several versions of samplers designed to exert a constant force on a defined area in a wiping action. These methods have potential for simulating the transfer of mass and are non-destructive. One such monitor is a fixed pressure dislodgeable residue sampler—such as a polyurethane foam roller.²² Ross *et al*⁴² used standardised movements (aerobic dance routines following an instructor and music) to measure transfer of pesticides from fogged carpets onto the **skin**.

Transfer from the inner clothing contaminant layer to the **skin** contaminant layer is

usually estimated with patches or underwear. No other method seems to have been developed specifically for measuring this transfer.

Removal

Dissipation of contaminants from the clothing compartment has been the subject of many studies, however, the studies were focused on the transport of mass from the clothing compartment to the **skin** compartment—that is, the opposite direction to removal. Yang and Li⁴³ reported a frictional transport of pesticides of 1%–5% from contaminated clothing to underwear. As mechanical or frictional transport may be an important mechanism of removal, these data indicate the range of mass transport from clothing in the opposite direction. Removal from skin to surface has been studied by Brouwer *et al.*⁴¹ They reported a mean removal efficiency of 38% during a single pressure contact of a contaminated hand with an uncontaminated flat surface.

Redistribution

Information on the area exposed and the redistribution of contaminant could be obtained by observation. However, the method of choice is the fluorescent tracer technique with a quantitative image analysis system.^{13–17} These methods have high spatial resolution.

Decontamination

Decontamination of the air compartment is the removal of mass from the air compartment by either local or general ventilation. Methods to assess the efficiency of ventilation in reducing the concentration of gaseous and particulate contaminants are well developed.⁴⁴ Decontamination of surfaces can be assessed by measuring the mass removed—for example, the quantity of dust in a vacuum cleaner filter bag—or by the decrease in mass of the surface contaminant layer. A measurement strategy for decontamination of surface dust in offices has been described by Schneider *et al.*²¹ and a standard procedure to assess the efficiency of handwashing has been developed by Fenske and Lu.⁴⁵

Penetration and permeation

Penetration and permeation stand for transport of mass through either the clothing barrier or the stratum corneum. These mass transport pathways have been studied in great detail relative to the effectiveness of protective clothing⁴⁶ and percutaneous penetration.⁴⁷ In both cases a test cell design is used to measure permeation. However, several different methods are used in the assessment of percutaneous penetration ranging from in vitro models with static diffusion cells and flow through diffusion cells with animal or human skin (viable and non-viable).

General discussion and conclusions

In this paper we propose a conceptual model of both the important pathways leading to dermal exposure and the intermediate compartments where the hazardous substances may reside. This model has allowed us to define consistent

terminology, which should form the basis for improved comparability between studies of dermal exposure or surface contamination. Consistent use of the model will ensure that most appropriate variables are measured in any situation. The model has been constructed at a conceptual level and omits much of the detail, which is evident in real situations. It is possible to extend the model as a series of interlinked compartments for the **skin**, surfaces, etc. In this way compartments for hands, arms, torso, etc could represent the **skin** surface; or if greater resolution is required, fingers, palms, etc could represent the **skin** surface. In this way the existing model encompasses sufficient detail to enable terminology to be developed, and it could be generalised for any particular need.

The model can cope with special exposure scenarios—such as immersion of body parts in liquid or powder. In this case the liquid or powder constitutes the **skin** contaminant layer compartment and has infinite volume.

For interpretation of contaminated substances derived from soil and paste-like substances in the **skin** contaminant layer a refinement of the model is necessary. The **skin** contaminant layer could be subdivided into an outer layer and an inner layer in intimate contact with the stratum corneum. The possibility exists that it is the supply of hazardous substance from the outer layer to the inner layer, which limits the rate of uptake. This identifies a need to refine existing methods of measuring mass in the **skin** contamination layer compartment.

We have not considered the stratum corneum in much detail, as it is generally not available for surface sampling methods. **Skin** smpping with adhesive tape is a possible exception. Consecutive smpping allows semi-quantitative depth profiling, but if the **skin** contaminant layer is not empty, the mass in this compartment and in the **stratum** corneum will be partially mixed up. The finite thickness of the stratum corneum constitutes a buffer capacity and introduces a lag time for the transport process to reach equilibrium after a step change in concentration.²⁴ The lag time may vary from a few minutes up to days and its significance for risk assessment would be determined by duration of exposure compared with lag time.

The inventory of existing methods for measurement of **skin** and surface contamination (table 3) is only illustrative. Compilation of an exhaustive inventory and discussion relative to the model is beyond the scope of the present paper. However, with the model structure, limited or non-existing methods for measuring relevant compartment mass or transport processes have been identified:

- The model stresses the importance of measuring concentration in the **skin** contaminant layer but methods relevant for uptake are lacking

- The mass of particles in the **skin** contaminant layer may only have limited relevance for uptake. Particles are less likely to result in uptake than liquids and solubility of particles is an important qualifier which should be

specified along with results of measurements of the mass and composition of the skin contaminant layer

• A clear distinction must be made between mass in a compartment and transport of mass. Direct measurement of mass transport must be based on an appropriate theoretical model.

We envision that our paper will stimulate discussions and help in the development of more appropriate methods for the assessment and control of dermal exposure.

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Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations

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Abstract

Objectives—To investigate whether there is an excess of leukaemias in 0–15 year old children among those living in close proximity (within 100 m) of a main road or petrol station.

Methods—Data for 0–15 year old children diagnosed between 1990 and 1994 in the United Kingdom West Midlands were used. Postcode addresses were used to locate the point of residence which was compared with proximity to main roads and petrol stations separately, and to both together. Odds ratios (ORs) were calculated with solid tumours as a control, and incidence ratios (IRs) with population density as a control.

Results—The method based on solid tumours as a control showed ORs of 1.61 (95% confidence interval (95% CI) 0.90 to 2.87) and 1.99 (95% CI 0.73 to 5.43), for those living within 100 m of a main road or petrol station respectively. When population was used as a control, the estimated IRs for leukaemia were 1.16 (95% CI 0.74 to 1.72) and 1.48 (95% CI 0.65 to 2.93) for residence within 100 m of a main road or petrol station respectively, but neither reached significance at the 95% level. Results for residence in close proximity to both a main road and petrol station were inconsistent, but there were few. The influence of socioeconomic factors as represented by the Townsend deprivation index on leukaemia incidence was not significant and the results were not explicable on the basis of impact of social class.

Conclusions—The results are suggestive of a small increase in risk of childhood leukaemia, but not solid tumours, for those living in close proximity to a main road or petrol station. This increase in risk is not, however, significant and a larger study is warranted to establish the true risk and causes of any increase in risk.

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Keywords: leukaemia; children; road traffic; petrol station

It is now accepted that occupational exposure to high concentrations of benzene can lead to an excess of non-lymphocytic leukaemias.¹ For example, workers exposed to in excess of 400000 ppb-years benzene in the Goodyear Pliofilm plant showed a standardised mortality

ratio (SMR) of 6.64 (95% confidence interval (95% CI) 1.33 to 19.39).² Despite the fact that most leukaemias in children are of the acute lymphocytic variety, a type not associated with occupational benzene exposure, there have been suggestions that environmental exposure to benzene vapour may be a cause of childhood leukaemia. Wolff³ showed significant correlations between acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic lymphoid leukaemia, low grade non-Hodgkin's lymphoma, and all lymphoproliferative disease and the number of cars per household in each United Kingdom county. Wolff³ postulated that benzene exposure within the car might be responsible for these correlations. In a more complex study, Alexander *et al*⁴ estimated relative risks (RRs) for childhood acute lymphoblastic leukaemia by Poisson regression for groups of electoral wards classified by isolation and car ownership. Multivariate analyses include adjustment for socioeconomic status. No evidence of increased risk of childhood acute lymphoblastic leukaemia was found in areas where more households own cars. It was concluded that the previous explanation for the small area variation of childhood acute lymphoblastic leukaemia in terms of geographical isolation and interpretation in terms of exposure to common infections continued to be justified.

Other geographical analyses of risk of childhood cancer have looked for evidence of involvement of an infectious process^{5,6} or for an association of high risk with proximity to either nuclear or industrial installations.^{7–9} Apart from the well known excess of childhood leukaemias around the Sellafield nuclear reprocessing plant, none of the nuclear sites examined in England and Wales showed evidence of an increased risk of childhood leukaemias and non-Hodgkin's lymphomas in the area covered by a 25 km circle around each plant.⁸ Knox and Gilman⁹ found an association of increased risk of childhood leukaemias and solid cancers with proximity to a range of industrial sites. Relative excesses were consistently associated with proximity to sites producing two main types of industrial atmospheric effluent: (a) volatiles derived from petroleum, and (b) kiln and furnace smoke and gases, and effluents from internal combustion engines. However, no evidence was found of an association with proximity to benzene works.

Much is known about personal exposure to benzene. In the United States the total exposure assessment methodology (TEAM) study^{10,11} measured the sources of personal

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exposure, showing a wide range of sources including active and passive smoking, personal activities—such as use of paints, solvents, other consumer products, and refuelling the car, as well as breathing outdoor air and air in the car. Personal exposures generally exceeded, but were correlated with concentrations in outdoor air. In a study in the United Kingdom, Leung and Harrison¹² carried out both direct measurement and modelling of personal exposure to benzene and other monoaromatic hydrocarbons. The results showed that although some microenvironments—such as adjacent to petrol pumps when refuelling the car—showed highly increased concentrations, integrated personal exposure was influenced far more by microenvironments in which the subjects spent large periods, the home being the most important, with the workplace also being significant for those who worked outside the home. Measurements of the spatial distribution of benzene in the atmosphere have shown that the highest outdoor concentrations within urban areas tend to occur adjacent to main roads,¹³ or in the vicinity of petrol stations.¹⁴ The influence of such ground level sources usually extends for about 100 m before concentrations fall to the local background.¹⁵ This result derives from several monitoring and modelling studies of traffic generated pollutants in open country. The dispersion of pollutants in urban terrain is more complex, but none the less the same general guidelines can be expected to apply. Concentrations within houses are strongly influenced by those out of doors, and hence the occupants of homes located within 100 m of a main highway or petrol station would be expected to experience higher exposures to benzene and related hydrocarbons than occupants of comparable homes at greater distances from such sources.

As the epidemiological studies already referred to have not given a wholly consistent answer to the proposition that benzene exposure may influence incidence of childhood leukaemia, and some have been criticised on methodological grounds, it was thought appropriate to conduct a further analysis of incidence of childhood cancer relative to sources of hydrocarbons. In our study, residence within 100 m of a main highway or petrol station was taken as a surrogate for increased exposure to benzene and other hydrocarbons present in evaporative losses of petrol, or to exhaust emissions from road traffic.

Methods

CASES OF LEUKAEMIA AND SOLID CANCER

Data from the West Midlands Cancer Intelligence Unit for 0–15 year old children diagnosed between 1990 and 1994 were used. Cases were taken from the Birmingham, Walsall, Solihull, Dudley, Wolverhampton, and Sandwell District Health Authorities (total population 2 251 000) as full data on petrol stations were available only for these areas. Classifications from the ninth revision of the international classification of diseases (ICD-9) were included for lymphoid, myeloid, monocytic, and unspecified leukaemia, including

those of uncertain behaviour, and for solid cancers and benign neoplasms. In the United Kingdom all cancer registries, together with the Office for National Statistics use the ICD for both childhood and adult tumours to be consistent across databases rather than the international CCC 1996 coding classification.

GEOREFERENCING DATA USING THE UNIT POSTCODE AND CENSUS GEOGRAPHY

The areas of enumeration districts (EDs), wards and health authorities are used in the study for aggregation of data. The EDs are the smallest areas that can be used to use population census data. Wards are constructed from EDs and in the West Midlands have an average population of 15 600. Health authorities are constructed from wards and form the administrative areas by which health services are organised in the United Kingdom. To integrate data into a geographic information system, both the petrol stations and the cancer cases and controls were allocated a grid reference using their unit postcode. This was accomplished with a table called the Central Postcode Directory (CPD). This consists of all the postcodes in the West Midlands and their grid references. The postcodes from the cancer registration database are matched to identical entries in the CPD. A unit postcode (the full seven or eight digit version—for example, B15 2TT) represents about 13 household children in the West Midlands. Grid references were allocated to unit postcodes in the following way. A 100 m² grid is used to identify in which grid square the first household of a unit postcode is located. This unit postcode is then assigned the grid reference of the south west corner of the grid square. This means that all postcodes whose first house is situated in a particular grid square are allocated the same grid reference. If a postcode happens to be towards the north west of the grid square then the reference will be inaccurate. This inaccuracy was offset by adding 50 m to the easting and northing of the grid reference as recommended by Gatrell *et al.*¹⁶ and used in a study of cancer around a TV transmitter mast by Dolk *et al.*¹⁷

Full postal addresses of petrol stations operational in 1997 within the West Midlands were purchased from Thames Communications (Gravesend, Kent). The local authority planning departments provided information on the closure and construction of petrol stations during the period 1990–7, which allowed development of a database containing addresses of stations fully operational during the years 1990–4 inclusive. Each petrol station was then allocated a grid reference with Matchcode (a software package developed by Capscan, London). Matchcode can improve address data by adding a postcode if one is missing or improving the address if it is slightly inaccurate. At the same time it can add a grid reference to an address. This is done by the software referring to a CD ROM that contains all the addresses in the United Kingdom. This is called the Post Office address file (PAF) and is what the CPD is derived from. After the post-

code was allocated to the stations with Match-code, the 50 m adjustment was made.

The CPD is provided free to NHS organisations and Universities and is often used in geographical studies as a method of grid referencing postcodes. Resources are available that allow users to grid reference a postcode to an claimed accuracy of 0.1 m (ordnance survey address point product), but the expense of this product prohibits its use in the NHS and academia.

ROADS OF HIGH TRAFFIC DENSITY

Traffic flow data for the West Midlands was obtained from the Joint Data Team, Birmingham. This exists as counts of vehicles along links of road throughout the West Midlands. The data pertaining to the roads used in this study were extracted and average traffic flows calculated.

The Ordnance Survey dataset STRATEGI was used as a source for the digital road network. The following road categories were chosen as being of **high** traffic density: motorways, primary routes (dual and single carriageways), and single and dual carriageway A roads. In all, this selected 755 sections of road with mean traffic flow 23 400 vehicles a day (10% percentile 11 500; 90% percentile 38 800) as derived from the Joint Data Team statistics for the individual road links.

DATA ANALYSIS

Spatial analysis was performed with a geographic information system (ArcView V2.1). Other manipulation of data was carried out with the software package Microsoft Excel. To investigate prevalence of childhood leukaemia relative to locality of a petrol station and proximity of main roads, the geographic information system was used to perform two different kinds of spatial analysis with different control groups.

In the first kind of analysis, the spatial distribution of leukaemias was analysed with solid tumour cases as a control. Leukaemia and control cases were plotted (with grid references

obtained from addresses at the time of diagnosis) and a spatial query was then performed to determine the number of cases and controls within a 100 m radius of a petrol station or a zone 100 m from a main road. In the second kind of analysis, leukaemia cases, petrol stations, and main roads were again entered into the GIS. The number of new leukaemia cases within 100 m of a source was again evaluated, but further separated according to the District Health Authority area. To include the population data as a control, the method of Dolk *et al*¹⁷ was adopted. To calculate the expected number of leukaemia cases within 100 m of a possible source, a population for such an area has to be calculated. Actual population counts do not exist for small user defined areas so they have to be estimated. The Postcode to Enumeration District Directory from the Office of National Statistics was used which contains the number of household children in each unit postcode. With census information for the ED that the postcode falls in, an average number of people per household can be calculated. From this we calculate the number of people per postcode. Finally with ED census information the number of 0–15 year old children can be estimated.

Townsend deprivation indices were available for electoral wards from the NHS Executive West Midlands Regional Office. To evaluate any influence of socioeconomic factors, the leukaemia incidence was plotted against the Townsend score for each ward. The Townsend index¹⁸ is a measure of multiple deprivation calculated from census variables. High scores reflect severe deprivation. Some other researchers in the United Kingdom have used the Carstairs index derived from Scottish data, whereas the Townsend index is derived from English data. Both indices have four census variables, three of which are common to both, and we would not anticipate any main differences from the use of the Carstairs index.

STATISTICAL METHODS

Two different approaches were used to investigate whether an excess incidence of leukaemia was present around main roads or petrol stations. In the first method odds ratios (ORs) were calculated with a case-control method. Each subject was classified as positive or negative according to their proximity to a main road or petrol station and defined as a case if they had been diagnosed with leukaemia or a control if the diagnosis was of a solid tumour. The OR was then calculated according to equation (1) where A were patients with leukaemia living within 100 m of a road or petrol station; B were patients with solid tumours living within 100 m of a road or petrol station; C were patients with leukaemia living away from a road or petrol station; and D were patients with solid tumours living away from a road or petrol station.

$$OR = AD/BC \quad (1)$$

The 95% confidence interval (95% CI) for the OR was calculated from

Table 1 Population (0–15 years old) within each district health authority and estimated to live within 100 m of source

	Birmingham	Dudley	Sandwell	Solihull	Walsall	Wolverhampton
Total population in age range	217583	59297	59665	40263	54610	51170
Population living <100 m from petrol station	8760	2118	2739	760	3102	2221
Population living <100 m from major road	33226	9425	10137	3792	8958	8561
Population living <100 m from petrol station and road	5955	1332	1994	300	1900	1575

Table 2 Numbers of leukaemia and solid cancers relative to location of residence, and Calculated odds ratios (ORs)

Location of residence	Leukaemias	Solid cancers (controls)	OR	95% CI
Major road < 100 m	24	31	1.61	0.90 to 2.87
Major road > 100 m	106	220		
Petrol station < 100 m	8	8	1.99	0.73 to 5.43
Petrol station > 100 m	122	243		
Major road and petrol station < 100 m	3	1	5.91	0.61 to 57.3
Major road and petrol station > 100 m	127	250		
Total cases/controls	130	251		

Table 3 Incidence ratio (IR (95% CI)) of childhood leukaemia if living <100 m from source

	Petrol station				Roads of high traffic density				Petrol station and roads			
	Obs	Exp	IR	95% CI	Obs	Exp	IR	95% CI	Obs	Exp	IR	95% CI
Birmingham	4	2.6	1.54	0.42 to 3.92	14	9.8	1.43	0.79 to 2.40	1	1.8	0.56	0 to 3.22
Dudley	1	0.6	1.67	0 to 9.33	4	2.6	1.54	0.42 to 3.92	1	0.4	2.50	0 to 14.5
Sandwell	1	0.6	1.67	0 to 9.33	3	2.2	1.36	0.27 to 4.00	1	0.4	2.50	0 to 14.5
Solihull	0	0.2	—	—	0	0.8	—	—	0	0.1	—	—
Walsall	1	0.9	1.11	0 to 6.22	1	2.6	0.38	0 to 2.23	0	0.6	—	—
Wolverhampton	1	0.5	2.00	0 to 11.2	2	2.7	0.74	0.07 to 2.67	0	0.4	—	—
All districts	8	5.4	1.48	0.65 to 2.93	24	20.7	1.16	0.74 to 1.72	3	3.7	0.81	0.16 to 2.38

$$95\% \text{ CI} = \exp[\ln \text{RR} \pm 1.96(1/A + 1/B + 1/C + 1/D)] \quad (2)$$

An OR of 1.0 would indicate that there is no effect on incidence of childhood leukaemia of living in close proximity to main roads or petrol stations.

The second method used indirect age and sex standardisation to examine the observed number of cases of leukaemia around main roads and petrol stations compared with what would be expected for the population of the health authority as a whole. An incidence ratio (IR) of 1.0 would indicate that there is no difference between the observed number of cases in the exposed group and that which would be expected from the comparison population. We have chosen not to use the term standardised IR as full age distributions were not known and therefore full standardisation has not been carried out.

To estimate the IR, the number of leukaemias in the 0–15 age group expected within a region within 100 m for a petrol station or main road was first calculated from equation (3)

$$E_{\text{pet/road}} = (C_A/P_A)P_{\text{pet/road}} \quad (3)$$

where $E_{\text{pet/road}}$ = expected number of cases, C_A = total number of cases in District Health Authority A (0–15 year age group), P_A = total population of 0–15 year old children in District Health Authority A, $P_{\text{pet/road}}$ = population of 0–15 year old children residing within 100 m of petrol station or road.

The IR was then calculated from

$$\text{IR}_{\text{pet/road}} = O_{\text{pet/road}}/E_{\text{pet/road}} \quad (4)$$

where $O_{\text{pet/road}}$ = observed number of leukaemia cases within 100 m of a petrol station or road.

Due to the small number of cases, the 95% confidence interval on the observed number of cases was read directly from standard statistical tables applying to the Poisson distribution. These were used due to the non-integer nature of the expected values.

Additionally, the Poisson probability of from 0 to (r–1) cases of disease was calculated, where r is the number of observed cases, and λ is the expected number. Probability (n cases) = $e^{-\lambda} \cdot \lambda^n / n!$

These probabilities were summed from n=0 to n=r–1 and subtracted from 1.0 to give the probability of $\geq r$ events occurring.

Results

The study was limited to 0–15 year old children for several reasons. Most important is the relatively short time interval between disease induction and diagnosis which makes spatial analysis more realistic than for adult

cases. Secondly, important factors which can confound the analysis of adult cancer data are not present for children. Most important among these are smoking and occupational exposure to carcinogens. Childhood cases of cancer are also more accurately diagnosed and more completely registered than adult cancers."

Table 1 shows basic data relating to the populations within the six district health authorities which were included in this study. The area is densely populated and as many as 17% of the population were classified as residing within 100 m of a main road within some health authority areas. Table 2 shows the number of cases and controls according to location of residence when solid tumours were used as controls. The table also shows the ORs and 95% CIs for leukaemia relative to solid cancer. While we were conducting this study, the work of Knox and Gilman¹ showed that both leukaemias and solid tumours had similar excesses relative to the sources examined in that work. It was therefore thought prudent to use some other form of analysis, and with the procedures outlined above, estimated populations of 0–15 year old children were used to calculate expected numbers of cases of leukaemia. The results of this study expressed as IRs appear in table 3. This procedure was carried out also for solid tumours, showing for all districts combined IR values of 0.77, 0.8, and 0.24 for residences close to petrol stations, main roads, and the two jointly, respectively. None of these was significantly different from 1.0 at the 95% level.

Discussion

Both methods show an increased risk of childhood leukaemia for those living within either 100 m of a petrol station, or within 100 m of a main road. For the case-control method, standard 95% CIs appear in table 2. For the IR method, 95% confidence limits on the observed value were taken from statistical tables for the Poisson distribution, and used to calculate a 95% CI on the IR. Probabilities were calculated for the combined health authorities for proximity to a main road (p=0.28) and proximity to a petrol station (p=0.18). In neither instance, therefore, is the result significant at the 95% level although the data for all district health authorities together approach significance for the case-control method. This finding is broadly consistent with a study of the incidence of leukaemia and lymphoma in young people (0–24 years) within 3 km of the petrochemical plant at

Baglan Bay, South Wales." By contrast, a study in Britain by Knox and Gilman¹ found excesses near to sites producing two main types of industrial atmospheric effluent (petroleum derived volatiles; and kiln and furnace smoke and gases, and effluents from internal combustion engines), but a non-significant excess of childhood leukaemias and solid cancers near to petrochemical works, and no association of increased risk with proximity to benzene installations. Reasons for the differences in findings between studies may be related to problems obtaining accurate population denominators on which to base calculations of expected numbers or in the definition of exposed populations. The study in South Wales took as its exposed population those resident within EDs, wholly or partially within concentric circles of 1.5 or 3 km radius of the centre of works. This included areas outside these zones, and took no account of the wind direction frequencies and pattern of dispersion of gaseous effluents from the petrochemical plant. Because of the long period covered by cases used in the Knox and Gilman study (1953–80), census-based population estimates could not be used, and would not have been available at the fine spatial resolution required; instead a method based on postcodes was used.² This could have created a false apparent excess of cases near to industrial sources if postcodes close to those sources also systematically had higher densities of children living in them than did postcodes which were distant from industrial sources. Aware of this problem, the authors investigated the distribution of postcodes. Areas nearest to industrial sources had a lower density of postcodes per kilometre than other locations, indicating that fewer people lived in these postcodes, and hence that fewer cases would be expected in postcodes near to industrial locations. This, together with the consistency in the nature of the sites around which excesses were found, makes it unlikely that their findings were due to an artefact. None the less, some of the conclusions of Knox and Gilman are surprising. In particular, the finding of a relative excess of solid cancers and leukaemias within 4 km of a motorway, with a significant deficit beyond 4 km, is hard to reconcile with the fact that the impact of main roads on air quality is not measurable above the local background air pollution at distances beyond about 100–200 m.¹⁵ Our study was not without its problems, the population data for the 0–15 year age group was inferred from information for EDs which are considerably larger than postcode districts (by a factor of about 16). It was because of the uncertainties in defining exactly the population numbers in the exposed and control groups that we thought the case-control method would provide valuable supporting information. Another limitation of our study is the lack of age and sex standardisation. This is a problem for childhood cancers as previous studies have shown a slight increase of incidence for males relative to females (1.3:1 male to female ratio) and for the under 5s.¹⁹ Although main geographic

variations in the age and sex distribution of the 0–15 year old children within the West Midlands are unlikely, the lack of discrimination by age and sex may obscure aetiological insights which could be gained from a more refined analysis.

There is little published evidence to suggest that pollutant emissions from road traffic or petrol stations are connected with solid tumours in the general population, excluding occupationally exposed groups. Occupational exposure to polycyclic aromatic hydrocarbons is linked with an excess risk of lung cancer. As road vehicle emissions contain polycyclic aromatic hydrocarbons, adults residing alongside main roads may run a slightly increased risk of lung cancer from this source. This condition, however, represents only a tiny proportion of cancers in the 0–15 year age band for whom the brain and spinal cord are the main loci of solid tumours.²¹ Exposure to gasoline vapour in adult workers has been associated with an increase in kidney cancer? but this is also a rare condition in children. We therefore think it likely that solid cancers represent a good control for this study and that the ORs presented in table 2 represent a genuine representation of increased risk. The IRs for solid tumours show no excess risk and support this view. The combined use of the two complementary methods of data analysis in our view adds to the confidence with which the results can be viewed.

A plot of incidence of childhood leukaemia in 1000 children by electoral ward versus Townsend deprivation index shows a poor correlation ($r^2=0.04$; $n=130$), but there does seem to be a slight decrease in incidence of leukaemia with increased deprivation (higher Townsend index) as reported in previous studies.²³ In the West Midlands Health Region the more deprived wards tend to be sited in the central conurbation, whereas the more affluent wards tend to be in the rural shire counties. Thus, this finding is consistent with earlier findings of higher incidence of childhood leukaemia associated with lower population densities. It does not indicate any role for exposure to benzene from passive smoking in the aetiology of childhood leukaemia as smoking is more prevalent in homes of lower socioeconomic status (higher Townsend scores) and would produce the opposite slope to that found.

One question rarely, if ever, considered in the spatial analysis of disease in relation to pollution sources is the magnitude of exposure. Thus, many studies have related incidence of disease to distance from source without regard to the spatial distribution of pollutant concentrations. In this work the use of a criterion of 100 m separation between source and point of residence (as indicated by postcode) is consistent with knowledge of the range over which air pollution from a ground level source sustains concentrations above the local background. It is, however, extremely difficult to estimate the increased magnitude of exposure for those living within the 100 m band. The work of Leung and Harrison²⁴ shows that exposure within the

home is likely to be the main contributor to exposure to aromatic hydrocarbons, including benzene. The extent of exposure arising from the proximity of the road is very hard to estimate, but some indications can be gained from the work of Leung and Harrison.¹³ This work showed that roadside concentrations of aromatic hydrocarbons, including benzene, were highly variable depending on the sampling site. In particular, the openness of the site, and therefore the ease of pollutant dispersion, has a major influence on atmospheric concentrations. Taking the mean of 53 samples collected alongside six main roads in Birmingham indicates a typical ratio of roadside to urban background concentration of benzene of roughly 5, and for toluene roughly 2.5. Allowing for the fact that indoor concentrations often slightly exceed those out of doors due to indoor sources, and the slightly greater distance of most homes from the traffic than the roadside samplers used in the work of Leung and Harrison,¹³ it is likely that the exposure to benzene for those living within 100 m of a busy road is around twice that of those living at greater distance from the road. Long term average concentrations of benzene in the vicinity of petrol stations are broadly similar to those at the roadside, and therefore a similar magnitude of increase might be expected.

Petrol stations are unlikely to generate sufficient traffic on their own to cause a substantial increase in pollutants from vehicle exhaust. It might be expected that petrol stations would be located mostly on main roads, and the data in table 1 indicate that this is the case for >50% of the exposed population. The data for populations living within 100 m of a petrol station does, however, include a substantial additional population and justifies the separate treatment of this category of exposure. Petrol stations are most notable as a source of evaporated hydrocarbons from petrol. On the other hand, main roads are the source of a wider range of pollutants including nitrogen oxides and polycyclic aromatic hydrocarbons as well as volatile hydrocarbons such as benzene. If our finding of a higher RR associated with proximity to a petrol station than to a main road were borne out by a study of higher statistical power, it would be strongly suggestive of an influence of hydrocarbons upon childhood cancer.

The results of this study are broadly consistent with those of other published work. Savitz and Feingold²⁴ reported an OR of 1.7 (95% CI 1.0 to 2.8) for cancer among children exposed to more than 500 vehicles a day. They reported ORs also for leukaemia of 2.1 (95% CI 1.1 to 4.0) and brain tumours of 1.7 (95% CI 0.8 to 3.9). Their results showed a dose-response gradient with traffic in excess of 10 000 vehicles a day giving an OR of 3.1 (95% CI 1.2 to 8.0) for total cancer and of 4.7 (95% CI 1.6 to 13.5) for leukaemia. Feychting et al²⁵ used calculated nitrogen dioxide concentrations as an estimate of exposure to traffic pollution and found a relation between RR of cancer in 0-15 year old children relative to exposure to nitrogen dioxide. With those exposed to a 99 percentile of hourly average concentrations

over 1 year of nitrogen dioxide of $>49 \mu\text{g m}^{-3}$ defined as an RR of 1, those exposed to concentrations in the $50-79 \mu\text{g m}^{-3}$ range were subject to an RR of 1.9 (95% CI 0.8 to 4.5), and for a concentration of $\geq 80 \mu\text{g m}^{-3}$ the RR was 3.8 (95% CI 1.2 to 12.1). Increased but imprecise risk estimates were found for leukaemia and central nervous system tumours. Background concentrations of nitrogen dioxide in the United Kingdom West Midlands conurbation lie within the highest band (99 percentile $\geq 80 \mu\text{g m}^{-3}$) used in this study. These workers²⁵ also used data published by Wertheimer and Leeper²⁶ to calculate the association between traffic density and childhood cancer from a study designed to investigate the association between exposure to electromagnetic fields and childhood cancer where traffic density was included for control of confounding. In this study exposure to heavy traffic was defined as homes within 40 m of road with a daily traffic count of ≤ 5000 . The effect of thus defined heavy traffic on total cancer mortality in children was calculated as an OR of 1.6 (95% CI 1.1 to 2.3). Information for specific cancer sites was not provided. The results of these studies both for total childhood cancer and for leukaemias are broadly consistent with the result of our own research strongly suggesting that although the results are just below the level of significance normally required, they are reflective of a true effect of road traffic on cancer in children.

Conclusions

The total population of the area studied is 2.25 million and the population of 0-15 year old children included in the data analysis is 482 588. The study included all diagnosed cases of leukaemia in the 0-15 year age group over a period of 5 years. The results suggest a slight increase of risk of leukaemia for those 0-15 year old children living in close proximity to a main road or petrol station, although in no case do the results reach significance. The two methods used based on use of solid tumours and population numbers as controls give broadly similar results except in the case of proximity to both main road and petrol station where the number of cases is very small and the results have very wide 95% CIs. Exposure of the population within 100 m of source is likely to be of the order of double that of other dwellers within the conurbation not living in such high proximity. In the case of petrol stations, increased exposures are primarily to hydrocarbons, including benzene, whereas in the case of main roads, pollutants include combustion products such as NO_x and polycyclic aromatic hydrocarbons as well as volatile hydrocarbons such as benzene. The fact that increased risks are found at both kinds of site (although not significant) is suggestive of volatile hydrocarbons as a causal agent. Although the results of the study are suggestive of a possible slight association of exposure to pollutant (not necessarily benzene) with increased incidence of leukaemia, the data are overall rather reassuring in showing that any such effect, if real, is likely to be small in magnitude. A larger

study is warranted to establish whether there is **truly an increase in risk for those living in close proximity to roads and petrol stations and to determine the causes.**

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Rejected manuscripts

From February 1994, authors whose submitted articles are rejected will be advised of the decision and one copy of the article, together with any reviewer's comments, will

be returned to them. The *Journal* will destroy remaining copies of the article but correspondence and reviewers' comments will be kept.

Risk of stomach cancer associated with 12 workplace hazards: analysis of death certificates from 24 states of the United States with the aid of job exposure matrices

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Abstract

Objective—To investigate the risk of gastric cancer associated with 12 workplace exposures suspected or discussed as aetiological agents in previous reports.

Method—A case-control study was conducted based on the death certificates of several million deaths in 24 states of the United States in 1984–96. Overall, the data base included 41 957 deaths from stomach cancer among subjects aged ≥ 25 years. These were 20 878 white men, 14 125 white women, 4215 African American men, and 2739 African American women. Two controls for each case were selected from among subjects who died from non-malignant diseases, frequency matched to cases by geographic region, race, sex and 5 year age group. Each three digit occupation and industry code listed in the 1980 United States census was classified for probability and intensity of exposure to asbestos, inorganic dust, metals, lead, polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, nitrosamines, sulphuric acid, fertilisers, herbicides, other pesticides (including insecticides and fungicides), and wood dust. These job exposure matrices were subsequently applied to the occupation-industry combinations in the death certificates of study subjects, separately by sex and race.

Results—Risk of stomach cancer showed a modest association with occupational exposure to inorganic dust (odds ratio (OR)=1.06; 95% confidence interval (95% CI) 1.03 to 1.11) with significant increasing trends by probability and intensity of exposure overall and by cross classification of the two exposure metrics. Workplace exposure to nitrosamines also showed a modest association (OR=1.06; 95% CI 1.01 to 1.11), but the excess risk was even smaller after adjusting for inorganic dust exposure. Risk of gastric cancer was not associated with any of the other workplace exposures considered in this study.

Conclusions—Non-differential misclassification of exposure may have caused negative findings in this study, and inorganic dust may be a partial surrogate for exposure to other unknown risk factors. Alternatively, our results suggest that occupational factors contribute little to the aetiology of gastric cancer. Inorganic

dust might act through non-specific mechanisms, similar to those proposed for salt, aspirin, and heat by other authors.

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Keywords: stomach; neoplasms; occupational exposure

In a review of occupational risk factors for stomach cancer we suggested that various occupational exposures may cause or contribute to gastric carcinogenesis. 'Ionising radiation and N-nitroso compounds, either directly or through the formation of free radicals or nucleophilic intermediates, may damage the DNA of the cells of the gastric mucosa, acting as initiators of the carcinogenic process. Other physical agents, such as asbestos and other inorganic dusts, could be irritants to the gastric mucosa and act as cocarcinogens in a way similar to the mechanism proposed for salt, aspirin, and heat.' These agents cause a superficial gastritis and may increase cell proliferation, thus promoting initiated clones. Dust could also act as a carrier delivering carcinogens to the gastric mucosa. The effectiveness of this mechanism has been experimentally proved in lung carcinogenesis.

A major cause of concern is that most studies of gastric cancer and occupation rely on poor environmental data. Often, only occupational titles are available to imply exposure to suspected gastric carcinogens. Even surrogates for exposure—such as duration of employment—are seldom used to calculate dose-response trends. Besides, small study size has been a limiting factor in interpreting findings. In the absence of industrial hygiene measurements, use of job exposure matrices, which has provided a useful tool in other studies,⁵ might be profitable. To test the hypothesis of a role of occupational risk factors in the aetiology of gastric cancer, we established job exposure matrices for 12 suspected gastric carcinogens in the workplace and applied them to the occupation-industry combinations in a large data base including death certificates from 24 states from the United States in 1984–96. Poor detail of the occupational information is still a concern in this study, but both the large size of the study population and the use of already designed job exposure matrices are new contributions.

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Methods

Since 1984, the National Cancer Institute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics have supported the coding of occupation and industry titles on death certificates from 24 states from the United States according to the 1980 United States census occupation and industry codes.⁶ Details on the data base of death certificates from 24 states of the United States have been reported elsewhere.⁷ We extracted data of 41 957 subjects who died from stomach cancer at age ≥ 25 from several million death certificates in 1984–96. These were 20 878 white men, 14 125 white women, 4215 African American men, and 2739 African American women. We used a case-control design to evaluate the association of risk of stomach cancer with 12 workplace exposures, separately by sex and race. Two controls for each case were selected from among subjects who died from non-malignant diseases, frequency matched to cases by geographic region, race, sex, and 5 year age group.

One occupation and industry is reported on the death certificate. Information on duration

or other characteristics of employment is not available. By applying job exposure matrices to the occupation-industry combinations in the death certificates of study subjects, we evaluated occupational exposure to 12 workplace hazards, that we previously discussed in a review on occupational risk factors for stomach cancer⁸—namely asbestos, inorganic dust, metals, lead, polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, nitrosamines, sulphuric acid, fertilisers, herbicides, other pesticides (including insecticides and fungicides), and wood dust. An estimate of intensity (none=0, low=1, medium=2, high=3) and probability (none=0, low=1, medium=2, high=3) of exposure to each of the 12 occupational hazards was developed by two authors (MD and PC) for each three digit 1980 United States census occupation and industry code. Intensity of exposure was estimated based upon industrial hygiene and occupational health textbooks,^{9,10} computerised exposure data bases (OSHA files, NIOSH inspections data base), unpublished industrial hygiene reports, and personal experience. The probability index was estimated based on the proportion of exposed

Table 1 Risks of stomach cancer by probability of exposure to suspected gastric carcinogens, by sex and race

Exposure	Study group	Unexposed (OR=1) (n)	Probability of exposure (n OR (95% CI))			
			Low	Medium	High	
Asbestos†	WM	16859		4007	0.97 (0.93 to 1.02)	22
	AAM	2856		1357	1.08 (0.99 to 1.17)	2
	WW	13356		769	1.06 (0.96 to 1.17)	0
	AAW	2538		201	1.19 (0.98 to 1.45)	0
Inorganic dust	WM**	11974	1361	2666	1.11 (1.05 to 1.17)	4877
	AAM*	1990	274	825	1.19 (1.07 to 1.32)	1126
	WW**	13482	175	337	1.22 (1.06 to 1.41)	131
	AAW	2558	28	71	0.90 (0.67 to 1.20)	82
Metals	WM	16572	662	2142	1.04 (0.98 to 1.10)	1502
	AAM	3473	120	448	1.01 (0.90 to 1.14)	174
	WW	13696	67	292	1.22 (1.05 to 1.41)	70
	AAW	2678	9	46	1.14 (0.79 to 1.65)	6
Lead	WM	17276	1572	527	1.01 (0.91 to 1.13)	1503
	AAM	3365	312	85	0.93 (0.72 to 1.21)	453
	WW	13753	224	83	0.90 (0.69 to 1.16)	65
	AAW	2677	43	9	1.37 (0.58 to 3.21)	10
Polycyclic aromatic hydrocarbons	WM	14232	1356	1896	1.06 (1.0 to 1.13)	3394
	AAM	2815	256	325	1.02 (0.88 to 1.17)	819
	WW**	13736	201	90	1.13 (0.87 to 1.46)	98
	AAW	2614	33	13	1.48 (0.72 to 3.02)	79
Nitrosamines	WM**	16478	792	2760	1.08 (1.02 to 1.14)	848
	AAM	3322	163	567	0.97 (0.86 to 1.09)	163
	WW**	13810	176	123	1.40 (1.11 to 1.78)	16
	AAW	2608	40	88	1.27 (0.96 to 1.69)	3
Nitrogen oxides	WM	14794	788	669	0.98 (0.89 to 1.08)	4627
	AAM	2835	216	219	0.98 (0.83 to 1.16)	945
	WW**	13815	147	38	1.35 (0.89 to 2.04)	125
	AAW	2612	37	8	1.48 (0.59 to 3.70)	82
Sulphuric acid	WM	15228	4531	675	1.12 (1.01 to 1.23)	444
	AAM	2678	1212	223	1.12 (0.94 to 1.33)	102
	WW	13128	675	310	1.02 (0.87 to 1.20)	12
	AAW	2103	219	416	0.96 (0.79 to 1.17)	1
Herbicides	WM	19190	146	19	0.91 (0.53 to 1.55)	1523
	AAM	3817	62	10	0.68 (0.33 to 1.40)	326
	WW	14062	5	4	2.10 (0.52 to 8.41)	54
	AAW	2688	1	0	—	50
Other pesticides	WM	18099	1104	121	1.05 (0.84 to 1.31)	1554
	AAM	3318	508	58	0.95 (0.69 to 1.30)	331
	WW	13930	110	23	0.87 (0.53 to 1.42)	62
	AAW	2634	43	12	0.71 (0.37 to 1.37)	50
Fertilisers	WM	19058	151	148	1.30 (1.06 to 1.60)	1521
	AAM	3760	37	100	0.95 (0.74 to 1.22)	318
	WW	14012	48	7	0.86 (0.36 to 2.08)	58
	AAW	2648	16	25	0.97 (0.59 to 1.57)	50
Wood dust	WM	19107	903	195	0.91 (0.77 to 1.08)	673
	AAM	3523	482	80	0.96 (0.73 to 1.26)	130
	WW	14022	75	22	0.71 (0.44 to 1.16)	6
	AAW	2715	18	6	1.33 (0.47 to 3.76)	0

*p<0.05; **p<0.01 test for trend.

†The reference group for subjects exposed to asbestos includes those with a low probability of exposure, due to the difficulty in estimating a baseline exposure.

WM=white men; AAM=African American men; WW=white women; AAW=African American women).

workers within a given job title or industry, and the number of occupations or industries coded likewise. To obtain one intensity and one probability score for a given exposure in each study subject, intensity and probability scores associated with the occupation and the industry were considered in two ways: (a) if information on exposure resulted from the occupation regard- less of industry—for example, plumber, or welder—we calculated the subject's intensity and probability scores as the square of the occupational score; (b) if industry was the main contributor to exposure assessment—for example, truck driver in the rubber industry, or labourer in the construction industry—then the subject's probability and intensity scores resulted from multiplying the respective scores attributed to the industry code. The rationale for squaring or multiplying scores in semiquan- titative retrospective exposure assessment has been described elsewhere.¹⁰ In the present study, the main scope of this strategy was to have individual scores in the same order of magnitude, whether deriving from occupation

only or from occupation and industry. The final scores of probability and intensity of exposure were further categorised within four levels (none=0, low=1-2, medium=3-4, high=6-9).

Odds ratios (ORs) were estimated by logistic regression, and 95% confidence intervals (95% CIs) with the GEMBO program in the Epicure software. Covariates included in the logistic regression model were age, ethnic origin (American, Hispanic, European, other, unknown), marital status (never married versus ever married), metropolitan versus non-metropolitan residence, and five categories of socioeconomic status based on Green's standardised score for specific occupations.¹¹ Statistical significance of trends in risk by increasing exposure intensity and probability was tested by assuming covariates as non-categorical, and subtracting from the result of the goodness of fit statistic, obtained when the exposure variable was not included in the logistic regression model, the result of the same statistic with the exposure variable. Under the null hypothesis, this test has a χ^2

Table 2 Risks of stomach cancer by intensity of exposure to suspected gastric carcinogens groups

Exposure	Study group	Unexposed (OR=1) (n)	Low intensity of exposure (n OR (95% CI))	Medium intensity of exposure (n OR (95% CI))	High intensity of exposure (n OR (95% CI))
Asbestos	WM	17783	2764	1.0 (0.95 to 1.04)	431
	AAM	3711	848	1.10 (1.0 to 1.20)	96
	AAW	13912	213	1.07 (0.90 to 1.26)	0
	WM**	2686	51	1.23 (0.86 to 1.75)	0
	AAW	11974	3002	1.07 (1.01 to 1.12)	1267
	WM**	1990	842	1.22 (1.10 to 1.36)	283
	AAW	13482	296	1.23 (1.06 to 1.42)	61
	WM**	2558	36	1.04 (0.69 to 1.57)	20
	AAW	16572	1509	1.04 (0.97 to 1.11)	1541
	WM**	3473	158	1.13 (0.97 to 1.31)	286
	AAW	13696	50	1.14 (0.97 to 1.34)	137
	WM**	2678	7	0.92 (0.57 to 1.49)	29
	AAW	17276	2168	0.96 (0.89 to 1.04)	290
	WM**	3365	556	1.10 (0.98 to 1.25)	110
	AAW	13753	170	1.09 (0.90 to 1.31)	57
	WM**	2677	24	1.82 (1.04 to 3.18)	35
	AAW	14232	1983	1.08 (1.02 to 1.15)	616
	WM**	2815	370	1.06 (0.92 to 1.23)	225
	AAW	13736	159	1.29 (1.06 to 1.59)	17
	WM**	2614	85	1.11 (0.84 to 1.46)	19
	AAW	16478	433	0.99 (0.88 to 1.12)	698
	WM**	3372	48	1.26 (0.87 to 1.82)	179
	AAW	13810	17	1.29 (0.70 to 2.38)	68
	WM**	2608	0	0.99 (0.94 to 1.04)	10
	AAW	14794	3636	1.01 (0.94 to 1.08)	1114
	WM**	2835	804	1.03 (0.89 to 1.19)	267
	AAW	13815	116	1.50 (1.17 to 1.91)	96
	WM**	2612	81	1.18 (0.88 to 1.57)	96
	AAW	15228	4113	0.99 (0.95 to 1.03)	263
	WM**	2678	1232	1.04 (0.96 to 1.14)	77
	AAW	13128	565	0.88 (0.79 to 0.98)	13
	WM**	2103	212	1.09 (0.90 to 1.32)	4
	AAW	19190	22	1.11 (0.65 to 1.88)	1574
	WM**	3817	4	1.07 (0.32 to 3.59)	377
	AAW	14062	7	4.09 (0.37 to 45.6)	53
	WM**	2688	0	0.61 (0.06 to 5.85)	50
	AAW	18099	652	1.14 (1.02 to 1.27)	1590
	WM**	3318	356	1.16 (1.0 to 1.34)	381
	AAW	19058	106	1.17 (0.92 to 1.48)	185
	WM**	3760	20	0.81 (0.48 to 1.36)	140
	AAW	14012	12	1.56 (0.73 to 3.34)	9
	WM**	2648	1	0.60 (0.06 to 5.78)	27
	AAW	19107	1	1.23 (0.89 to 1.71)	163
	WM**	3523	406	1.16 (1.02 to 1.33)	80
	AAW	14022	23	0.83 (0.51 to 1.35)	8
	WM**	2715	4	0.75 (0.24 to 2.36)	1
Wood dust	WM	17783	2764	1.0 (0.95 to 1.04)	431
	AAM	3711	848	1.10 (1.0 to 1.20)	96
	AAW	13912	213	1.07 (0.90 to 1.26)	0
	WM**	2686	51	1.23 (0.86 to 1.75)	0
	AAW	11974	3002	1.07 (1.01 to 1.12)	1267
	WM**	1990	842	1.22 (1.10 to 1.36)	283
	AAW	13482	296	1.23 (1.06 to 1.42)	61
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	AAW	13815	116	1.50 (1.17 to 1.91)	96
	WM**	2612	81	1.18 (0.88 to 1.57)	96
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	WM**	2678	1232	1.04 (0.96 to 1.14)	77
	AAW	13128	565	0.88 (0.79 to 0.98)	13
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	AAW	14062	7	4.09 (0.37 to 45.6)	53
	WM**	2688	0	0.61 (0.06 to 5.85)	50
	AAW	18099	652	1.14 (1.02 to 1.27)	1590
	WM**	3318	356	1.16 (1.0 to 1.34)	381
	AAW	19058	106	1.17 (0.92 to 1.48)	185
	WM**	3760	20	0.81 (0.48 to 1.36)	140
	AAW	14012	12	1.56 (0.73 to 3.34)	9
	WM**	2648	1	0.60 (0.06 to 5.78)	27
	AAW	19107	1	1.23 (0.89 to 1.71)	163
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	AAW	14022	23	0.83 (0.51 to 1.35)	8
	WM**	2715	4	0.75 (0.24 to 2.36)	1

*p<0.05; **p<0.01 test for trend.
 †The reference group for subjects exposed to asbestos includes those with a low intensity of exposure, due to the difficulty in estimating a baseline exposure.
 ‡The number of unexposed subjects differs between the two exposure metrics, as subjects may be attributed to different probabilities of intensity of exposure.
 WM=white men; AAM=African American men; WF=white women; AAW=African American women.

Table 3 Risks of stomach cancer by probability and intensity of exposure to asbestos, inorganic dust, metal dust, lead, nitrosamines, nitrogen oxides, PAHs, sulphuric acid, and fertilisers (white men)

Probability of exposure (n OR (95% CI))									
Intensity of exposure	All exposed		Low		Medium		High		Test for trend
Inorganic dust:									
All levels	8904	1.07 (1.03 to 1.11)	1361	0.98 (0.92 to 1.05)	2666	1.11 (1.05 to 1.17)	4877	1.08 (1.03 to 1.13)	p<0.01
None	11974	1.0	11974	1.0	11974	1.0	11974	1.0	
Low	4635	1.05 (1.0 to 1.10)	971	0.97 (0.90 to 1.06)	1124	1.09 (1.0 to 1.18)	2540	1.08 (1.01 to 1.16)	p<0.01
Medium	3002	1.07 (1.01 to 1.12)	302	1.04 (0.91 to 1.20)	1125	1.13 (1.04 to 1.22)	1575	1.03 (1.0 to 1.10)	NS
High	1267	1.13 (1.05 to 1.21)	88	0.94 (0.73 to 1.22)	417	1.10 (0.97 to 1.25)	762	1.18 (1.08 to 1.30)	p<0.01
p Value test for trend	<0.01		NS		<0.01		<0.01		
Metals:									
All levels	4306	1.05 (1.0 to 1.09)	662	1.05 (0.96 to 1.16)	2142	1.04 (0.98 to 1.10)	1502	1.06 (0.99 to 1.13)	p=NS
None	16572	1.0	16572	1.0	16572	1.0	16572	1.0	
Low	1256	1.02 (0.95 to 1.09)	359	1.06 (0.93 to 1.21)	683	1.0 (0.91 to 1.10)	214	1.01 (0.86 to 1.20)	p=NS
Medium	1509	1.04 (0.97 to 1.11)	268	1.06 (0.91 to 1.23)	857	1.02 (0.94 to 1.11)	384	1.06 (0.94 to 1.21)	p=NS
High	1541	1.09 (1.02 to 1.16)	35	1.01 (0.67 to 1.51)	602	1.12 (1.01 to 1.24)	904	1.07 (0.99 to 1.17)	p<0.05
Test for trend	0.01		NS		0.05		NS		
Nitrosamines:									
All exposed	4400	1.06 (1.01 to 1.11)	792	1.01 (0.93 to 1.10)	2760	1.08 (1.02 to 1.14)	848	1.05 (0.97 to 1.15)	p<0.05
None	16478	1.0	16478	1.0	16478	1.0	16478	1.0	
Low	433	0.99 (0.88 to 1.12)	201	0.94 (0.79 to 1.11)	169	1.05 (0.87 to 1.27)	63	1.06 (0.78 to 1.45)	p=NS
Medium	3474	1.06 (1.01 to 1.11)	487	1.01 (0.90 to 1.13)	2313	1.07 (1.01 to 1.14)	674	1.04 (0.94 to 1.14)	p<0.05
High	493	1.16 (1.03 to 1.30)	104	1.21 (0.95 to 1.54)	278	1.16 (1.0 to 1.35)	111	1.12 (0.89 to 1.41)	p=NS
p Value test for trend	<0.01		NS		<0.01		NS		
Sulphuric acid:									
All levels	5650	1.01 (0.97 to 1.05)	4531	1.0 (0.96 to 1.04)	675	1.12 (1.01 to 1.23)	444	0.96 (0.85 to 1.08)	p=NS
None	15228	1.0	15228	1.0	15228	1.0	15228	1.0	
Low	4113	0.99 (0.95 to 1.03)	3624	0.99 (0.95 to 1.04)	144	1.13 (0.92 to 1.39)	345	0.91 (0.80 to 1.04)	p=NS
Medium	1274	1.03 (0.96 to 1.11)	845	1.04 (0.95 to 1.13)	408	1.05 (0.93 to 1.19)	21	0.79 (0.48 to 1.30)	p=NS
High	263	1.23 (1.05 to 1.44)	62	0.93 (0.68 to 1.26)	123	1.42 (1.12 to 1.79)	78	1.29 (0.97 to 1.72)	p<0.01
p Value test for trend	0.01		NS		<0.05		NS		

n=Number of exposed cases.

distribution with a single degree of freedom, and it probes specifically linear trends in log relative risk with increasing exposure.¹² p Values were two tailed.

Results

Mean age at death from stomach cancer was lower among men than among women and among African Americans than white people (African American men: 67.3 (SD 13.0); African American women: 71.4 (SD 14.6); white men: 69.4 (SD 12.3); white women: 74.2 (SD 12.8)). Compared with controls, cases were more often married in all four study groups, and they defined their ethnic origin (mainly European, or Hispanic) twice as often as controls among white men and white women. Other variables—such as metropolitan residence and socioeconomic status—did not show a consistent frequency distribution by case-control across the four study groups (not shown in the tables).

Risks by probability of exposure to 12 occupational risk factors combining all levels of exposure are shown in table 1. None of the investigated exposures showed an unequivocal trend in all study groups. Only inorganic dust

and nitrosamines were associated with ORs >1.0 for the high probability of exposure category in all four study groups. Two of the four risks associated with high probability of exposure to inorganic dust were significant and another was of borderline significance. Although absolute increases in risk were small, trends for probability of exposure to inorganic dust were significant among white men, white women, and African American men, and for exposure to nitrosamine among white men and white women.

Table 2 shows risks by intensity of exposure to the same 12 occupational risk factors. High intensity exposure to the risk factors was rare among women. However, a significant positive trend in at least one study group was found for inorganic dust, metals, nitrosamines, nitrogen oxides, and sulphuric acid. Again, although absolute risk increases were small, the significant trends by intensity of exposure to inorganic dust and nitrosamines among white men replicated similar findings that used probability of exposure.

Patterns of increasing risk of stomach cancer by probability within intensity category and vice versa were explored for inorganic dust, metals, nitrosamines, and sulphuric acid (table 3). Although excess risks were quite small, trends by probability of exposure to inorganic dust were significant in low and high categories of intensity, and trends by intensity of exposure were significant for subjects classified in the medium and high probability of exposure. Results were less consistent for metals, nitrosamines, and sulphuric acid. No such pattern was found for exposure to the other workplace

Table 4 ORs (95% CI) for stomach cancer associated with any exposure to inorganic dust, metals, nitrosamines, and sulphuric acid and for all the other exposures and by marital and socioeconomic status, and metropolitan residence

Exposure	OR	95% CI
Inorganic dust	1.05	1.0 to 1.10
Metals	1.01	0.96 to 1.07
Nitrosamines	1.04	0.99 to 1.09
Sulphuric acid	0.99	0.95 to 1.03

Table 5 Risks of stomach cancer by probability and intensity of exposure to inorganic dust among subjects unexposed to metals and nitrosamines (white men)

Probability of exposure (n OR (95% CI))							
Intensity of exposure	Low		Medium		High		p Value test for trend
Inorganic dust:							
Unexposed	10955	1.0	10955	1.0	10955	1.0	
Low	701	0.93 (0.84 to 1.02)	705	1.23 (1.10 to 1.38)	180	0.96 (0.80 to 1.15)	NS
Medium	59	0.94 (0.69 to 1.28)	293	1.13 (0.97 to 1.30)	680	1.01 (0.91 to 1.12)	NS
High	13	1.14 (0.58 to 2.24)	59	1.10 (0.80 to 1.51)	359	1.20 (1.04 to 1.38)	<0.01
p Value test for trend	NS		NS		<0.05		

hazards considered in this study. To see whether reciprocal confounding was responsible for some of the observed associations, we combined all categories of exposure and fitted a model with the basic variables plus exposure to inorganic dust, metals, nitrosamines, and sulphuric acid to reciprocally adjust the respective risk estimates. As reported in table 4, this analysis resulted in a very modest increase in risk of stomach cancer for exposure to inorganic dust and to nitrosamines, but no excess risk was associated with ever exposure to metals and sulphuric acid.

Cross tabulation of probability and intensity of exposure to inorganic dust among workers unexposed to metals and to nitrosamines showed significantly positive trends by probability in the high intensity category and by intensity in the high probability category (table 5). The analysis of such a risk pattern among subjects with isolated exposure to metals or to nitrosamines did not provide interpretable results due to small numbers and empty cells.

Among white men, the most numerous occupation contributing to the excess risk associated with high probability and high intensity of exposure to inorganic dust was mining machine operators represented by 1.34% cases and 1.25% controls. Other less numerous contributing occupations were: plasterers (0.05% cases and 0.04% controls), concrete and terrazzo finishers (0.12% cases and 0.07% controls), mining occupations not elsewhere classified (0.10% cases and 0.09% controls), excavating and loading machine operators (0.04% cases and 0.03% controls), and crushing and grinding machine operators (two cases and no controls). In the same study group, the most represented industry contributing to the excess risk of stomach cancer in the high probability and high intensity of exposure to inorganic dust was mining and quarrying (1.49% cases and 1.35% controls). Coal mining, metal mining, and non-metallic mining and quarrying contributed equally to the modest excess risk. Other contributing industries were: construction (0.21% cases and 0.13% controls), and structural clay products (three cases and three controls).

Discussion

In this large case-control study based on death certificates from 24 states from the United States we found a modest association of risk of stomach cancer with occupational exposure to inorganic dust. Although the increase in risk was modest, increasing trends were calculated by

probability and intensity of exposure overall and by cross classification of the two exposure metrics. Other suspected risk factors for gastric cancer did not show the same association or showed a even weaker association after adjustment for exposure to inorganic dust. Our data do not provide information about whether ingestion of generic inorganic dust or specific dust components play a part in gastric carcinogenesis. Therefore, one possible explanation for our findings is that exposure to inorganic dust may have behaved as a partial surrogate for exposure to other unknown risk factors. Alternatively, dusty workplace environments could play a non-specific role in gastric carcinogenesis. If the association were confirmed with exposure to generic inorganic dust, a plausible explanation would be that physical properties of dust might be important, by causing local irritation or absorbing gastric carcinogens on its surface and delivering them to the target cells in the gastric mucosa. Such a mechanism was experimentally proved long ago in lung carcinogenesis.¹

Previous case-control studies have reported an association between occupational exposure to dust and stomach cancer:¹³⁻¹⁵ not explained by ethnicity¹³ or diet.⁵ Results were less consistent for a role of specific dusts. A case-control study based on the Los Angeles County cancer registry found the greatest increase in risk of cancer of the antrum or pylorus for exposure to mineral dust.¹⁴ The association was also found in an Italian multi-centre case-control study of 640 histologically confirmed male cases of stomach cancer,³ although no attempt was made to investigate subsites in more detail. In a large multicancer site, multifactor case-control study in Montreal, Canada, silica was the only inorganic dust,¹⁶ and wood the only organic dust¹⁷ to show a positive association with stomach cancer. Disentangling exposure to silica from other inorganic dust would require additional information on workplaces and possibly industrial hygiene measurements, which was not the case in the present study. On the other hand, we did not find an association with wood dust, the only organic dust we tested, and trends associated with exposure to metals (which included dust and fumes) were less consistent than with the more generic category of inorganic dust (including also metal dust). Exposure to lead was not associated with a risk of stomach cancer, and adjustment for exposure to inorganic dust weakened the positive association found with nitrosamines. Cross

tabulation of probability and intensity of isolated exposure to nitrosamines did not provide further clues, because of small numbers and empty cells. Endogenous synthesis of nitrosamines from dietary precursors was suggested as the crucial event in gastric carcinogenesis.⁹ Exposure to nitrosamine precursors or to preformed nitrosamines in the work environment was also suggested as a possible explanation for the repeatedly found increase in risk of gastric cancer in industries where such exposures may occur.⁹ Further study including monitoring of exposure to nitrosamines in the work environment and in biological fluids of exposed workers are warranted.

Occupational exposures in agriculture, such as to herbicides, other pesticides, and fertilisers, were not associated with a risk of gastric cancer in this study. A review of cancer among farmers suggested a possible increase in risk of stomach cancer.¹⁶ The epidemiological evidence for this seems to be conflicting,⁹ and confounding by rural residence was suggested as a possible explanation.⁹

Limitations in this study are mainly related to the poor occupational information that may be extracted from death certificates and the insufficient specificity of the coding system. Use of the most prevalent occupation and industry in the working history of each person as reported in the death certificate may result in important loss of information on exposures experienced in other jobs, mainly among short term workers who usually experience the highest workplace exposures.¹⁷ Besides, the three digit census code of occupations and industries may incorporate very heterogeneous workplace conditions within the same code, which prevents a reliable classification of exposure. Although this characteristic was considered in classifying occupations and industries by probability of exposure, a substantial amount of non-differential misclassification could have affected our results, which could have lowered the association between stomach cancer and occupational exposure to inorganic dust.¹⁸

Among possible confounders, ethnic origin, marital status, and socioeconomic status were included in the logistic regression model. As rural residence is another important confounder in occupational studies of stomach cancer,⁹ but an urban or rural characterisation of residence was not available from the death certificates, we used metropolitan versus non-metropolitan residence as a surrogate. Region of residence was controlled for by matching cases and controls. The analysis was conducted separately by race and sex groups. As controlling for diet was not possible, residual confounding may have biased our findings in cases of important differences in dietary habits associated with the occupational exposures considered in this study.

Gastric cancer risk is reportedly correlated with low educational level and low socioeconomic status.^{19, 20} Therefore, risks associated with exposures typical of occupations classified in the lower socioeconomic groups, such as inorganic dust, might have been affected as

well. Low socioeconomic status was not associated with stomach cancer risk in our study, which was conducted using a death certificate data-base. This source of information is not suitable to evaluate the association between low socioeconomic status and mortality from specific diseases, as bias can result from a more accurate definition of the cause of death and a lower mortality from all causes among the wealthier socioeconomic groups. As a consequence, in our study, when socioeconomic status was not included as a covariate in the logistic regression model to adjust risk estimates, risks associated with intensity and probability of exposure to inorganic dust were 1.0 or very close to unity, and no positive trend was found (not shown in the tables). On the other hand, risk associated with high probability of exposure to inorganic dust was increased in three out of four socioeconomic groups comprising exposed cases (lowest socioeconomic status: 1.12; second lowest socioeconomic status: 1.11; medium socioeconomic status: 0.89; medium to high socioeconomic status: no cases; highest socioeconomic status: 1.08), although linear increases with probability of exposure were found **only** in the two lowest socioeconomic groups. Odds ratios for high intensity exposure to inorganic dust were increased in three socioeconomic groups (no cases and no controls were classified in this cell among the medium to **high** and the highest socioeconomic status category), and linear increases in risk with intensity of exposure were found in the second lowest and medium socioeconomic status (not shown in the tables). Therefore, low socioeconomic status was not an explanation for the modest increase in risk of stomach cancer associated with exposure to inorganic dust found in our study.

In conclusion, our results confirm previous reports of an association between occupational exposure to inorganic dust and risk of stomach cancer. Further research is warranted to explore mechanisms and dose-response relations possibly with measurements of environmental dust.

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