Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review

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Aim To identify those agents reported as being associated with reactive airways dysfunction syndrome (RADS).

Methods A systematic review was undertaken. Abstracts were screened and those selected reviewed against pre-determined diagnostic criteria for RADS.

Results Significant information gaps were identified for all measures of interest. In some articles, even the causative agent was not reported. The most commonly reported agents were chlorine (nine subjects), toluene di-isocyanate (TDI) (n = 6) and oxides of nitrogen (n = 5). Most exposures occurred in the workplace (n = 51) and affected men (60%). Dyspnoea (71%) and cough (65%) were the commonest symptoms. Median symptom duration was 13 months (interquartile range = 6.5–43.5) for RADS.

Conclusions Although the most commonly reported agent associated with RADS was chlorine, the main finding of a general lack of adequate information on exposure, investigation and outcome suggests that to better explore RADS a more structured approach to gathering information is required. A minimum data set for reporting RADS cases is proposed.

Key words Asthma; irritant-induced asthma; reactive airways dysfunction.

Background

Twenty years ago, Brooks coined the term ‘reactive airway dysfunction syndrome’ (RADS) [1] which he defined as symptoms simulating asthma within 24 h of a single, massive, chemical exposure. The United Kingdom surveillance of work-related and occupational respiratory disease (SWORD) survey found that the prevalence of asthma in those who had had an acute irritant exposure varied, apparently affected by the intensity and length of acute exposure, the duration of follow-up and the suspected agent [2]. As the agent involved in RADS may affect prognosis, the authors aimed to assess the range of agents implicated in RADS.

Methods

A systematic review of RADS using Brooks’ criteria (see Figure 1) was undertaken. Studies were included if subjects suffered from RADS as defined by Brooks. Reactive airways dysfunction was defined (see Figure 1) as requiring a documented absence of preceding respiratory complaint with symptom onset occurring after a single specific exposure incident to a gas, smoke, fume or vapour present in very high concentrations which had irritant qualities to its nature. Further, Brooks required that the onset of symptoms occurred within 24 h after the exposure and persisted for at least 3 months, that symptoms simulated asthma (cough, wheezing, chest tightness and dyspnoea) and that while pulmonary function tests might show airflow obstruction, methacholine challenge testing was positive and other types of pulmonary disease were ruled out. Studies were excluded if they contained no cases meeting Brooks’ RADS criteria or were duplicate publications or follow-up studies.

Studies were identified by searching MEDLINE, EMBASE and CINAHL from 1985 to 2005 (limited to English language and further limited to human research for EMBASE and MEDLINE) supplemented by review of references of recent review articles and original reports. The search was complemented by hand-searching conference abstracts published in the American Review of Respiratory and Critical Care Medicine, European Respiratory Journal and Thorax from 1985 onwards. Keyword search terms included reactive airways dysfunction...
Recommended minimum data set for reporting RADS

**Parameters**

**Exposure**
- Substance (if known)
- Description of circumstances of exposure
- Location (work/home/environmental)
- Duration of exposure
- Frequency (single or multiple)

**Individual**
- Age
- Gender
- Smoking history
- Atopy
- Occupation

**Treatment**
- Timing of treatment initiation
- Therapy given
- Duration of therapy

**Outcome**
- Assess treatment outcome at:
  - 3 months
  - 6 months
  - 12 months
  - 18 months
  - 24 months and every 12 months thereafter

**Response to treatment**
- Symptoms (resolution/partial response/no benefit)
- Spirometry – measured values of FEV₁, FVC
- Occupational outcome (Return to work/changed job/unemployed)
- Bronchial reactivity – measured values of bronchial reactivity

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**Clinical criteria for the diagnosis of reactive airways dysfunction (RADS) (Brooks 1985)**

1. A documented absence of preceding respiratory complaint.
2. The onset of symptom occurred after a single specific exposure incident or accident.
3. The exposure was to a gas, smoke, fume or vapour present in very high concentrations and had irritant qualities to its nature.
4. The onset of symptoms occurred within 24 hours after the exposure and persisted for at least three months.
5. Symptoms simulating asthma (cough, wheezing, chest tightness and dyspnoea)
6. Pulmonary function tests may show airflow obstruction.
7. Methacholine challenge testing was positive.
8. Other types of pulmonary disease were ruled out.

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Figure 1. Flow chart showing on the left the suggested minimum data set for reporting any case of reactive airways dysfunction and on the right Brook’s diagnostic criteria referred to in this review.

syndrome, irritant-induced asthma, toxic gas inhalation, non-immunologic asthma or irritant gas.

Two people (M.S.S. and F.D.D.) reviewed all titles and abstracts to exclude studies that failed to meet inclusion criteria. Full texts selected were reviewed to exclude studies where the patient did not have RADS. Disagreements on three cases were resolved by discussion. A single reviewer (M.S.S.) extracted data on the causative agent or agents, exposure level, duration of overexposure, location of accident, number of cases, symptom onset, symptoms, symptom duration, the provocation concentration causing a 20% fall (PC₂₀) in forced expiratory volume in 1 s after inhalation of methacholine or histamine, forced expiratory volume in 1 s (FEV₁%), FEV₁/forced vital capacity ratio (FVC), variation of peak expiratory flow, treatment onset, treatment type, treatment response, atopy and, where undertaken, biopsy results. After data extraction, results were entered on separate tables for each category of data (e.g. PC₂₀, FEV₁%) extracted.

**Results**

Eighty-four articles and abstracts were found but 25 of the articles identified either contained no cases meeting RADS criteria or were duplicate publications or follow-up studies and so were excluded. Among the 633 cases described in the 59 articles selected, 63 cases met Brooks’ criteria and 570 had insufficient data for allocation to RADS (Appendix 1). Of the 63 RADS cases, 38 (60%) were male, 12 (19%) female and in 13 (21%) gender was not reported. The mean age in this group was 37.8 (SD 11.6) years but age was not reported for seven people.

The most common agents in patients who met Brooks’ criteria were chlorine (nine subjects), TDI (six subjects), oxides of nitrogen (five subjects), acetic acid (four subjects), sulphur dioxide (four subjects) and paint (four subjects) [1].

The most frequent location of exposure episode in those with RADS (n = 63) was the workplace (n = 51) with others occurring in the environment (eight subjects), home (three subjects) and not reported (one subject). The proportion of non-atopic patients was higher than atopic patients but for 41% of RADS group atopic status was not reported.

The onset of symptoms in Brooks’ group occurred immediately (within 1 h) in 29 patients and within 24 h in 34 patients. In one article that reported 20 cases [3], the onset of symptoms in 17 cases occurred within 24 h.
and in three cases within 1 week. It is unclear in which of those cases symptoms began within 1 week. As it was not possible to categorize these 20 patients, they were excluded.

Dyspnoea, cough and wheeze were the most common symptoms. Seventy-one per cent of RADS subjects had dyspnoea (n = 45), 65% cough (n = 41), 43% wheeze (n = 31), 43% chest tightness (n = 27), 29% upper respiratory irritation (n = 18), 25% eye irritation (n = 16), 16% mucus production (n = 10) and 6% cyanosis (n = 4). In the RADS group, symptom duration was recorded in all cases. The median and interquartile range (IQR) for symptom duration in patients who met Brooks’ criteria was 13 (6.5–43.5) months.

Of 63 patients who met Brooks’ criteria, 19 (30%) were smokers with a median (IQR) consumption of 11 (7–18) pack-years, 7 patients (11%) were ex-smokers with a median (IQR) consumption 5 (5–10.8) pack-years and 21 (33%) patients were non-smokers. In 16 subjects with RADS (25%), no information was given about smoking.

Information regarding FEV1% was available for 49 of the 63 (78%) subjects with RADS. Among these 49 subjects, 16 subjects (33%) had an FEV1% <80%, the median (IQR) for FEV1% being 63% (55.5–75). FEV1/FVC ratios were available for 44 of the 63 patients (70%) meeting Brooks’ criteria and in 23 of these 44 cases (52%), the ratio was <80%. The median FEV1/FVC ratio was 69% (64.3–71.8).

**Key points**
- There was a general lack of adequate information on exposure, investigation and, in particular, outcome of reported cases or case series of RADS.
- The most commonly reported agent associated with RADS was chlorine with TDI and oxides of nitrogen next most common.
- We suggest that a web-based database of RADS (and irritant-induced asthma) cases be established which would allow continuous update and better analysis of outcome in these individuals.

**Conflicts of interest**
None declared.

**Discussion**

The most commonly reported agents in the literature associated with a diagnosis of RADS were chlorine, TDI and oxides of nitrogen. The agents most frequently implicated in RADS were as anticipated although this list is likely to be incomplete as many cases of RADS may go unreported. It is possible that a degree of publication bias exists as once an agent has been first reported thereafter single case studies are less likely to be published and so the relative contribution of some agents to the overall burden of RADS may be underestimated. As these reports are essentially descriptive papers such suspected publication bias cannot be formally tested. However, the main finding was the remarkable inconsistency in the information provided, which in many cases did not permit a diagnosis of RADS despite being reported as such. In >40% of all cases, data were missing. In five articles, the causative agents were not stated.

Information on outcomes in relation to exposures needs to be collected formally and in a structured way if better advice and understanding of these conditions is to be gained. It is proposed that the data listed in Figure 1 constitute a minimum data set for reporting of RADS cases in the medical literature. A web-based reporting system with a database that could be updated online to permit the reporting and follow-up of cases would be of benefit and would deal to some extent with the issue of publication bias.

In summary, a systematic review of agents reported as being associated with RADS has been undertaken. The key finding is a lack of complete reporting of relevant information which limits generalization from, or summary of, these reports. As a consequence, a minimum data set for reporting RADS in the literature is proposed.

**References**

8. Brooks SM, Hammad Y, Richards I, Giovinco-Barbas J, Jenkins K. The spectrum of irritant-induced asthma: sudden...


43. Cormier Y, Coll B, Laviolette M, Boulet LP. Reactive airways dysfunction syndrome (RADS) following exposure to...


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Appendix 1: Papers included in systematic review and agents implicated in RADS

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>RADS exposures (No.)a</th>
<th>Cases not meeting Brooks’ criteria (No.)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brooks [1]</td>
<td>1985</td>
<td>Uranium hexafluoride, floor sealant, spray paint (3), 35% hydrazine, heated acid, fumigating fog, metal coat remover, fire/smoke</td>
<td></td>
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<tr>
<td>Gilbert [28]</td>
<td>1989</td>
<td>Dust or mold in silo (fungus)</td>
<td></td>
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<tr>
<td>Luo [12]</td>
<td>1990</td>
<td>Sodium hydroxide, silicon tetrachloride, trichlorosilaneb (2)</td>
<td>TDI (2)</td>
</tr>
<tr>
<td>Promisloff [20]</td>
<td>1990</td>
<td>Sodium hydroxide, silicon tetrachloride, trichlorosilaneb</td>
<td></td>
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</tbody>
</table>
## Appendix 1: (Continued)

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>RADS exposures (No.)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cases not meeting Brooks' criteria (No.)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demeter [29]</td>
<td>1990</td>
<td>Sulphuric acid, unknown</td>
<td>Lithium bromide, hydrogen chloride, cleaning solvent, zinc chloride (11)</td>
</tr>
<tr>
<td>Saric [31]</td>
<td>1991</td>
<td></td>
<td>Respiratory irritant such as hydrogen fluoride (30)</td>
</tr>
<tr>
<td>Angelillo [17]</td>
<td>1992</td>
<td>Chlorine (3)</td>
<td>o-chlorobenzylidene malononitrile</td>
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<tr>
<td>Hu [33]</td>
<td>1992</td>
<td>Sodium azide (2), epoxy resin, household cleaner containing morpholine</td>
<td></td>
</tr>
<tr>
<td>Blanc [34]</td>
<td>1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palczynski [35]</td>
<td>1994</td>
<td>TDI</td>
<td>Sulphur dioxide, hydrogen sulphide, acetic acid, hydrogen peroxide, chlorine, chlorine dioxide, hydrogen sulphide, methyl mercaptan, sulphur dioxide, hydrogen peroxide (2)</td>
</tr>
<tr>
<td>Chan-Yeung [36]</td>
<td>1994</td>
<td></td>
<td>Chlorine (12), nitrogen dioxide (3)</td>
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<tr>
<td>Gautrin [37]</td>
<td>1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palczynski [38]</td>
<td>1994</td>
<td>Sodium hypochlorite and hydrochloric acid (chlorine)&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Tarlo [40]</td>
<td>1995</td>
<td></td>
<td>Isocyanates (8), acid (3), acrylate (2), solvents, fume (2)</td>
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<tr>
<td>Sallie [41]</td>
<td>1995</td>
<td></td>
<td>Chlorine (9), sulphur dioxide (4), oxides of nitrogen (3), phosphine (2), ammonia (2), hydrogen sulphide, hydrogen chloride gas, sodium hydroxide, sulphuric acid, chloracetyl chloride, sodium fumes, hypochlorite, carboxylic acid, cleaning agents (3), combustion products (3), isocyanate (3), epoxy resin, glutaraldehyde, azodicarbonamide, aromatic amine, enzymes, trichloroethylene (3), methylene chloride, paint, pesticide, lubrication oil, unknown chemical (Pentamidine)</td>
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<tr>
<td>Stanbury [42]</td>
<td>1996</td>
<td>Sulphur dioxide (4)</td>
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<tr>
<td>Cormier [43]</td>
<td>1996</td>
<td>Hydrogen sulphide</td>
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<tr>
<td>Weiss [18]</td>
<td>1996</td>
<td>Sodium azide and hydrozoic acid&lt;sup&gt;b&lt;/sup&gt; (2)</td>
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<tr>
<td>Schonhofer [19]</td>
<td>1996</td>
<td>Chlorine (3)</td>
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<tr>
<td>Lemiere [44]</td>
<td>1996</td>
<td>Isocyanates mixed with organic solvent</td>
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<tr>
<td>Yelon [45]</td>
<td>1996</td>
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<tr>
<td>Lemiere [46]</td>
<td>1997</td>
<td>Chlorine</td>
<td></td>
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<tr>
<td>Burns [47]</td>
<td>1997</td>
<td>Bromine and hydrobromic acid (2)</td>
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<td>Provencher [48]</td>
<td>1997</td>
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<td>Forrester [16]</td>
<td>1997</td>
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<tr>
<td>Leroyer [50]</td>
<td>1998</td>
<td>Diphenylmethane diisocyanate</td>
<td></td>
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<tr>
<td>Conrad [51]</td>
<td>1998</td>
<td>Dinitrogen tetroxide (5)</td>
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### Appendix 1: (Continued)

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<tr>
<th>First author</th>
<th>Year</th>
<th>RADS exposures (No.)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cases not meeting Brooks’ criteria (No.)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatkin [6]</td>
<td>1999</td>
<td>TDI (4), isocyanate, chlorine, spray paint</td>
<td>Methyl mercaptan, solvent, glue&lt;sup&gt;b&lt;/sup&gt;, solvent, acrylate&lt;sup&gt;b&lt;/sup&gt;, TDI, isocyanate Bromine Bromotrifluoromethane, hydrogen fluoride, hydrogen bromide, carbonyl fluoride, carbonyl bromide&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Woolf [53]</td>
<td>1999</td>
<td></td>
<td>Bromine</td>
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<tr>
<td>Langley [54]</td>
<td>1999</td>
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<tr>
<td>Hill [55]</td>
<td>2000</td>
<td></td>
<td>o-chlorobenzylidene malononitrile (CS)</td>
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<tr>
<td>Meyer [56]</td>
<td>2001</td>
<td></td>
<td>Hydrogen fluoride, nitric acid&lt;sup&gt;b&lt;/sup&gt;, aldehydes, acetic acid&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Dube [57]</td>
<td>2002</td>
<td></td>
<td>Fume from an iron smelting process</td>
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<tr>
<td>Kopferschmitt-Kubler [58]</td>
<td>2002</td>
<td></td>
<td>Acid (4), chlorine (3), isocyanate (3)</td>
</tr>
<tr>
<td>Perfetti [59]</td>
<td>2003</td>
<td></td>
<td>Diphenylmethane disiocyanate</td>
</tr>
<tr>
<td>McLaughlin [60]</td>
<td>2003</td>
<td></td>
<td>Chlorine (2), rubber fume, sewerage gas, ammonia, propionic acid, NH4 and sorbic acid&lt;sup&gt;b&lt;/sup&gt;, ethanol, isopropanol, gingerine&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Piirila [22]</td>
<td>2003</td>
<td>Thermal decomposition products of CFC(2)</td>
<td>Nickel, Petroleum fraction (2), smoke (3), diisocyanates (2), soldering fume, caustic acids, dry wall powder, solvents (5), glues, 2-butoxyethanol, styrene-maleic anhydride resin, isopropanol, herbicides, sulfur dioxide, Petroleum distillate, Copier toner, Safrotin, Chemicals (NOS) (4), Ethyl acrylic, Sewer cleaner chemicals, paint fumes, diesel fuel, sodium hydroxide, chlorine, dazoin, gasoline, diesel fuel, ethylene glycol&lt;sup&gt;b&lt;/sup&gt;, ammonia, acids, bases, oxidizer (NOS)&lt;sup&gt;b&lt;/sup&gt;, muriatic acid, ethanolamines, indoor air pollutant</td>
</tr>
<tr>
<td>Henneberger [61]</td>
<td>2003</td>
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<td>Some selected agents</td>
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<tr>
<td>Franzblau [14]</td>
<td>2003</td>
<td>Hydrofluoric acid</td>
<td>Cleaning agent (42)</td>
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<td>Rosenman [62]</td>
<td>2003</td>
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<td>Banauch [63]</td>
<td>2003</td>
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<td>World trade centre fume (20)</td>
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<td>Gorguner [64]</td>
<td>2004</td>
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<td>Sodium hypochlorite and hydrochloric acid (chlorine) (55)&lt;sup&gt;b&lt;/sup&gt;</td>
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</table>

<sup>a</sup><sup>n</sup>1 except where otherwise indicated.

<sup>b</sup>Indicates exposure to multiple agents.