

# **IRRITANT INDUCED ASTHMA AND RADS**

**A short report prepared for EPAQS**

**April 2004**

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## **Summary**

A single high exposure of a person to an irritant chemical by inhalation, typically as an accidental incident involving a gas or vapour, can mean they run the risk of developing a type of asthma called reactive airways dysfunction syndrome or RADS. These people have irritable bronchial tubes and this hypersensitive state may last for some years. In many cases (although not all) it is much more resistant to treatment than conventional asthma but is a relatively rare condition; fewer than one in a thousand of all cases of asthma starting in adulthood are RADS. The condition has not been reported in children.

More recently, it has been suggested that lower levels of exposure to irritant substances repeatedly over time may also lead to the development of asthma. As it is possible that the biological processes involved in these people are similar to those seen in RADS, the general term irritant induced asthma (IIA) has been applied to this condition, a term which now includes RADS itself. Little is known of the outcome for IIA in general, but it is unlikely that it differs substantially from that in conventional asthma. Although outdoor air contains substances which, at high dose, have been known to cause RADS, levels of exposure to the population breathing outside air on a day-to-day basis are very much lower than those which would result in RADS. Consequently, although in theory persistent exposure to low levels of substances which at high dose can cause RADS could themselves lead to the development of asthma, it is most unlikely that this occurs in the population at large.

## 1 Terminology and definition

1.1 The term, reactive airways dysfunction syndrome (RADS) was first coined by Brooks in 1985 (Brooks *et al*, 1985) when he produced fairly strict criteria for an asthmatic-like state occurring within 24 hours of an acute, very high dose exposure and the presence of bronchial hyper-responsiveness to methacholine. In 1995 a consensus statement on asthma in the workplace (Chan-Yeung, 1995) suggested that these strict criteria should be relaxed slightly and a more comprehensive term introduced, namely irritant induced asthma (IIA). The criteria for IIA were laid down as:

- absence of previous respiratory complaints;
- onset of asthma symptoms within 24 hours of a single exposure to a high concentration of respiratory irritant gas;
- persistence of asthma symptoms for at least 3 months after exposure;
- symptoms associated with increased bronchial responsiveness and/or the presence of airflow obstruction with reversibility to broncho-dilator in the absence of previous lung disease.

1.2 This definition would cover all forms of IIA, including classical RADS and low-dose exposure to irritants over time. This issue of a changing definition was highlighted in a recent review of the area (Tarlo, 2003), where it was recognised that some authors included multiple acute exposures as causing IIA, some allowed up to a week after exposure for the onset of symptoms to occur, and some allowed lesser degrees of exposure – so called low-dose RADS or “not so sudden IIA” in their definition of IIA (Brooks *et al*, 1998). The possibility of exposures such as those which are recognised to lead to RADS/IIA could cause a stepwise worsening of patients with pre-existing respiratory disease is plausible but does not fall under these definitions. However, in the context of considering the health effect of the specific ambient exposures considered here, this should be regarded as possible although difficult to prove.

1.3 This raises the issue of non-peak irritant exposures to gases, fumes and some dusts as a cause of airways disease but, while the causal pathways may be real, the evidence is based on isolated reports or small series. However, this concept fits with reports of asthma developing in cleaners and workers chronically exposed to solvents (Medina-Ramon *et al*, 2003; Rosenman *et al*, 2003) and is consistent with the finding that 18% of cases of occupational asthma reported to the SHIELD Scheme in the West Midlands were due to irritants (Gannon & Burge, 1993). More recently a European survey (Kogevinas *et al*, 1999) also showed similar associations in workers exposed to irritants. In the occupational setting, small but above normal exposures have been reported to result in accelerated fall in FEV<sub>1</sub> and enhanced bronchial responsiveness (Gautrin *et al*, 1999).

1.4 If accepted, this variation in the diagnostic criteria for IIA will lead to differences in assessment of its prevalence. Estimates depending upon the diagnostic criteria used, range from 2-3% (Brooks *et al*, 1985; Tarlo & Broder, 1989) up to 18% (Ross & MacDonald, 1996).

- 1.5 From the point of view of environmental exposures, the possibility that longer-term exposures to chemicals might lead to asthma is therefore of great relevance when deciding about air quality standards. However, there are no usable data to aid our deliberations in this regard.
- 1.6 The SWORD database has had 301 cases of halide exposure resulting in respiratory disease reported to them, with an estimate of the likely total UK number being 477 between 1989 and 2003. Using the estimated UK figures, 338 were due to chlorine, 130 to HCl (either as gas or acid) and 9 to bromine. Most were recorded simply as inhalation accidents (with presumably no medium to long term sequelae) but 69 (20%) of those exposed to chlorine were reported to have developed asthma (whether irritant or sensitised) as did 26 (20%) of those exposed to HCl. The commonest occupational group exposed was chemical, gas and petroleum operators (10% for chlorine, 8.5% for HCl). This implies that a substantial minority of those exposed to either of these agents in an acute high dose develop an asthma type syndrome as a result, but these exposures are generally assumed to be far higher than any ambient exposures other than those encountered as spills/leaks.

## **2 Pathology**

- 2.1 There is very little difference if any between the histological appearances of IIA/RADS and conventional occupational asthma. There is some suggestion that in RADS there is less airway eosinophilic infiltration and more fibrosis (Brooks *et al*, 1985) but data are very limited.
- 2.2 It is possible that specific exposures may lead to reproducible patterns of IIA, such as exposures to chlorine (Chan-Yeung *et al*, 1994; Gautrin *et al*, 1994). In one such worker (Lemiere *et al*, 1997) who underwent bronchial biopsies on four occasions, initial epithelial desquamation with fibrinous exudate was followed by proliferation of basal cells and regeneration of the epithelium leading to collagen deposition in the submucosa with basement membrane thickening (Boulet *et al*, 1997) which might explain the attenuated airflow limitation reversibility seen in RADS. These steps were confirmed in animal models (Demnati *et al*, 1998) but, interestingly, inflammatory cells do not seem to play an essential role. However, this proposed model is not consistently supported in larger studies (Glindmeyer *et al*, 1997).
- 2.3 The association of what appears to be IIA in rescue workers involved in the destruction of the World Trade Centre (Prezant *et al*, 2002) suggests that this condition merely represents the final common pathway of a number of patterns of insults resulting in persistent airway irritative symptoms but with no specific underlying pathology.

## **3 Risk Factors**

- 3.1 Specific risk factors may contribute to the development of IIA. The most important causal factor is the dose of the agent as the nearer individuals are to a spill, the greater is the risk of developing RADS (Jajosky *et al*, 1999; Renisch *et al*, 2001). Current cigarette smoking and atopy also appear to be risk factors although less strongly than has been identified for conventional occupational asthma.

## 4 Prognosis

- 4.1 In classical RADS, the tendency is for improvement to occur over time, although in many individuals symptoms continue for years. There is much less evidence about what happens with IIA more broadly although the implication is that this is a much more permanent state of affairs. However, as yet, there are no longitudinal studies in these particular groups.
- 4.2 In one follow up study (Malo *et al*, 1994), normalization of FEV<sub>1</sub> and PC<sub>20</sub> to methacholine in approximately 25% of subjects after two and a half years was seen, the time course of recovery being similar to occupational asthma with a latency period, the maximum improvement occurring in the first two years.
- 4.2 Treatment is based on conventional asthma therapy but the response is often poor raising the issue of whether this should be regarded as more of a COPD/bronchitic picture rather than asthma. There is very limited information on treatment of the condition the role of oral steroids being debatable although apparently conferring some protection in a mouse model (Das *et al*, 1993).

## 5 Summary

- 5.1 In summary, IIA is probably commoner than has been thought; is associated with acute high exposures to irritant substances (not just gases); and has a variable prognosis, with some people being disabled for some years after exposure. In general terms, the response to anti-asthma therapy is disappointing.
- 5.2 Longer term exposure to lower levels of irritants may also lead to the development not only of asthma but a COPD/bronchitis picture in exposed workforces (Balmes, 2002). The inference of this observation is that environmental exposures, at an appropriate level, might also be contributing to the development of airways disease in the community. However, the data on dosing is very limited and at this stage it would probably be unwise to infer that ambient (i.e. low level) exposures to gases or fumes which at high level are known to cause RADS, might contribute to the burden of airways disease, although this remains a distinct possibility.

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