Appendix

Definitions and differential diagnoses

Asthma

Asthma (as defined by the Global Initiative for Asthma, GINA) is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role [1]. The chronic inflammation increases airway responsiveness, which leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread variable airflow obstruction that is reversible either spontaneously or with treatment.

Asthma arising from immunological reactions is called allergic asthma [2, 3]. Typically, this condition has a latency period, and the immunological mechanism has been identified for most high- and for some low-molecular weight (LMW) agents, i.e. anhydrides, isocyanates. These particular cases are initiated by IgE antibodies (IgE-mediated asthma). The relevance of immunological mechanisms in the absence of IgE-sensitization is not proven and needs further investigation.

The mechanisms initiating irritant-induced (non-allergic) asthma (whether with or without a latency period) are not well defined although similar inflammatory changes do occur. For details, see below.

Work-related asthma (WRA)

WRA comprises occupational as well as work-aggravated asthma [4].The pathophysiological mechanisms of OA do not differ from non-OA and it can also be separated into subdivisions following the same principle.

From the diagnostic point of view, it is important to divide OA into three subgroups:

- Allergic (IgE-mediated) OA. These cases comprise in most countries the majority of OA disorders and IgE antibodies are detectable that are specific for the causative occupational agent as indicated by an immediate-type skin-prick test. Examples include flour, animal proteins, molds, enzymes, latex, as well as some LMW agents (anhydrides, isocyanates) that elicit such responses in some individuals.
- OA due to unknown pathomechanisms. This includes OA due to wood dust, platinum and often isocyanates. IgE antibodies are not detectable even if there is a latent period, i.e. an asymptomatic period of exposure before the development of asthma until impairments occur.

- Irritant-induced OA. This disorder is caused by non-specific irritant or even toxic effects on the airways.

One subcategory of irritant-induced asthma is observed at high concentrations causing the disorder in most or even all occupationally exposed subjects. This is Reactive Airways Dysfunction Syndrome (RADS), now usually called acute irritant-induced asthma, which results typically from a single spill of chlorine, glutaraldehyde, isocyanates, ammonia, formaldehyde, acrylates or extremely high levels of dust or smoke (Table 2). Affected individuals have no pre-existing asthma, and asthma starts within 24 hours of the exposure together with increased non-specific hyperresponsiveness, persisting for at least three months after the incident. There is no latent interval, and those affected are not affected by usual low-dose exposure to the causative agent. If the exposure was at work, subsequent employment is not usually threatened (provided endangering exposures are excluded).

A further subcategory of Not so sudden irritant-induced asthma is due to lower concentrations of irritants, mostly in their occupational exposure limit (OEL) or permissible exposure limit (PEL) ranges. Exposures are less intense than in acute irritant-induced asthma. There is evidence for an excess of atopics and those with childhood asthma in this group. Those affected are not affected by usual low-dose exposure to the causative agent.

There is evidence for a third subcategory of irritant asthma, Low-dose irritant-induced asthma, which obviously has been overlooked for long time, although repeatedly reported [5, 6]. There is chronic or repeated exposure to a single irritant or mixture of irritants frequently below its/their OEL(s)/PEL(s) but no high-level exposure and asthma develops after a symptomless latent interval which may be several years. Once asthma has developed usual exposures result in asthma, similar to OA with sensitization. This is clinically indistinguishable from allergic OA in terms of pre-existing asthma, latency, atopy, smoking, NSBHR and the PEF responses to usual level exposure. Low-dose irritant-induced asthma was described in swine confinement facilities, comprising endotoxins [7, 8], exposure to cleaning agents [9, 10] including quaternary ammonium compounds, solvents, ozone, formaldehyde, chlorine, bisulfite and SO2, acid mist [11–15], diesel exhaust [16], fumigant residues [17], dusts in the textile paper, mineral fiber or construction industries [11, 18] or in mines [19]. It also encompasses at least some cases with potroom [20] and meatwrappers' asthma. Asthma in cold-air athletes may be another example [21, 22]. A paper from Hansson [23] summarized the literature on respiratory effects including asthma due to irritants levels below their occupational or permissible exposure limits (OELs/PELs), confirming that adherence to these limits does not always completely exclude work-related asthma from

occurring in susceptible subjects. Few exposure standards have been set with sensitization as their outcome, as most were originally based upon their irritant properties in normal volunteers and subsequently reduced following clinical or epidemiological studies that continued to show low-dose respiratory effects [23], as well as population-based studies [10, 13, 24–29]. More in general, exposure limits may have been derived from animal experimental evidence and findings from such studies have to be extrapolated to humans. Such extrapolations are usually accompanied by uncertainties. In contrast, others have questioned whether such low concentrations really do cause OA [30, 31]. These different opinions about the pathogenetic role of chronic or recurrent exposure(s) to low concentrations of respiratory irritants may be due to inclusion or exclusion of increased susceptibility in a small group of workers. Since there is limited scientific evidence for this disease entity so far, the task force wishes to encourage research groups to perform more detailed studies in this particular area.

Table 2 summarizes the distinguishing features of the three subcategories of irritant asthma.

Table 2: Subcategories of irritant-induced OA

Subcategories of irritant OA	Exposure concentration	Duration of exposure
Reactive airways dysfunction syndrome (RADS)	Extremely high, » OEL	< 1 day
Not so sudden onset of irritant OA	Moderate, OEL range	> 1 day and <4 months|
Low dose irritant OA	Low, below OEL	> 4 months

Related disorders

Asthma-like symptoms are not well-characterized and are not usually associated with a significant impairment in lung function but may represent an early stage of an increased susceptibility for work-related asthma. They should, therefore, be acknowledged in any preventive measures.

It is obvious that many substances causing work-related asthma also elicit work-related rhinitis and these include mainly high molecular weight particulate aeroallergens, e.g. from natural latex or flour, but also some LMW agents; e.g., acid anhydrides, which do cause occupational rhinitis as well as asthma [32–35]. Work-related rhinitis includes the following nosologic entities:

- work-related rhinitis caused by aeroallergens (allergic work-related rhinitis) or irritants in the workplace [36, 37],
- rhinitis which worsens at work (work-aggravated rhinitis) [38–43].

Allergic work-related rhinitis is frequently associated with NSBHR and often precedes work-related asthma, for which it was found to be a risk factor [32, 34, 36, 44–48], and, therefore, has to be considered when identifying risk groups for medical surveillance and for preventive measures in work-related asthma [38].

Work-related chronic cough is often associated with asthma or COPD, but only as a symptom, and represents a prevalent work-related airway disease that may precede the development of WRA [49, 50].

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