

Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area Is Azodicarbonamide (ADCA) a respiratory sensitiser?

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Introduction

The DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) proposes maximum workplace concentrations (MAK values) for volatile chemicals and dusts and recommends further classifications and designations.

This poster illustrates the recent evaluation of the sensitising potential of azodicarbonamide (ADCA) and the decision not to designate it as a substance causing airway sensitisation although ADCA is included into the Candidate List of Substances of Very High Concern (SVHC) by the European Commission considering its classification as a respiratory sensitiser

Criteria for the evaluation of respiratory allergens

Designation if sufficient evidence ... is provided by valid data from:

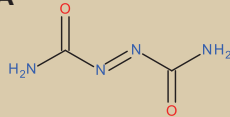
- studies or case reports of a **specific hypersensitivity** of the airways or the lungs which are indicative of an **immunological mechanism**
- from more than one patient and at least two independent centres and the symptoms ... must be shown to be associated with the exposure to the substance

No designation if:

- in spite of **extensive** handling of the substance, **very few** (well documented) cases of sensitisation are observed

The chemical ADCA

- ADCA is used in the rubber and plastics industries as a blowing agent in the expansion of a wide range of polymers including PVC, polyolefins and natural or synthetic rubbers
- During processing at about 200 – 215°C ADCA decomposes into gaseous compounds (nitrogen, carbon monoxide, carbon dioxide, ammonia) and non-volatile residues such as biurea, urazole, isocyanuric acid or cyanuric acid
- There is no more production of ADCA in the EU. The amount imported into the EU is in the range of 10 000-100 000 t per year



The chemical ADCA

- Since 1977 cases with **respiratory symptoms** related to exposure to ADCA were reported
- Binding of ADCA to proteins has been postulated and the proposed mechanism is a „Michael-addition“ to the **highly reactive** N=N-double bond that is activated by the 2 carbonyl residues
- Reaction with free amino-groups may be questioned as ADCA would preferentially react with weak and easily polarisable nucleophiles like thiols/thiolates
- In blood (in vitro), ADCA is reduced within minutes leading to oxidation of free thiol-groups e.g. in proteins; reaction is limited by the capacity of SH-groups

Case Reports

	Case reports with documented diagnostic			Case reports with less well documented diagnostic				
literature / cases	Malo et al. 1985 1	Malo et al. 1985 1	Kim et al. 2004 1	Normand et al. 1989 1	Normand et al. 1989 1	Normand et al. 1989 2	Valentino 1985 1	Ferris et al. 1977 6-9 (?)
latency	„several months“	„few months“	7 years	10 years ?	2 months ?	no ? (exposure 2 w/y)	1 year	„shortly“
provocation method / negative controls	„from 1 tray to another“ using lactose-ADCA-mixture 1:1 yes (1)			?	?	-	a) moving glass plate b) workplace related provocation	workplace related provocation no
prov. time	15 sec	15 sec	10 min	40 min	40 min	-	60 min and during shift	working shift
late reaction	yes	dual	(yes) (continuous reaction with max. after 5 h)	no until 4 h (patient reported reaction at night)	(yes) (continuous reaction with max. after 3-4 h)	-	a) No b) yes (4 h after end of shift)	decrease of mean FEV1 over shift measured on 3 days
max. fall of FEV1 / inspec. bronchial hyperreactivity ↑	-24% yes (2→0,28 mg)	-26% und -23% no (0,5→1,2 mg)	-22% (yes) (5 [or 0,9 ?]→0,5 mg)	(- < 7%) -	- 22% -	-	a) negative b) up to -50% -	FVC Ø -17%, -5%, -6% FEV1 Ø -21%, -8%, -10%
prick- / patchtest	-	-	neg. / pos.	-	-	-	-	-
other symptoms	eye irritation	rhinitis	-	eczema	eczema	1 x eczema	rhinitis	-

Exposure / Causality

- The **identity/purity** of the ADCA as used in provocation tests is not documented in any case report!
→ the real aetiopathogenic exposure is not definitely known
- The **fine dust particles**, possibly in combination with other factors (especially in the plastics industry) may also be causative
- Causality of **decomposition or pyrolysis products** has not been evaluated in the plastics industry
- Further exposure scenarios** may be involved, regarding information e.g. from some patent literature

Exposure / Causality

- ADCA is **usually compounded with some other ingredients** (e.g. ZnO, ZnO₂, chromium(III) salts or chromates) in order to modify the decomposition temperature
- Dicarboxylic acid anhydrides (such as succinic anhydride, glutaric anhydride, as well as known respiratory sensitizers like phthalic anhydride or trimellitic anhydride) are probably used as „desiccants“
- In the procedure of „chemical embossing“, the decomposition of ADCA is (partially) inhibited by such organic anhydrides or by acid hydrazides

Respiratory sensitisation - Summary

- In spite of some shortages, 3 case reports from 2 centres give **some evidence for an immunological mechanism** and could therefore be regarded as sufficient to (just shortly) fulfill the criteria for marking ADCA with „Sa“ as further case reports are inconclusive and/or insufficiently documented
- Regarding the (former) **relatively wide distribution/exposure**, these few cases provide only little evidence for a relevant sensitising potential
- No allergological diagnostics** have been done in „epidemiological“ studies“ from the working place (4 studies from 3 plants) and no such information is available for cases from *registration systems* (e.g. SWORD in GB)
- Evidence for a sensitising effect is contradicted by **mechanistic considerations** and by the **negative result in the LLNA**, which is in contrast to almost all known low molecular weight respiratory allergens
- There are (possibly) several alternative causes due to a **highly suspected co-exposure** (additives, decomposition or pyrolysis products) especially in the plastics industry
- For the overall assessment, it is essential that the **identity of the causal exposure is not clear cut documented**

➤ **The DFG MAK-Commission concluded that a respiratory sensitising effect of azodicarbonamide is not sufficiently proven and the substance has therefore not been marked with „Sa“.**

References: <http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>