



IFA

Institut für Arbeitsschutz der
Deutschen Gesetzlichen Unfallversicherung

Safety information on sensitising drug substances: the **BESI** project



Sensitising drug substances at workplaces

- Employees in the pharmaceutical industry involved in drug production
- Healthcare workers who use the drugs for therapeutic purposes:
 - Preparation and administration may cause sensitising effects



Problem: risk assessment of medicinal products at the workplace is difficult

- Medicinal products in the finished state are excluded from mandatory marking of hazardous substances (CLP Regulation)
- SDS (Safety Data Sheets) are generally available only for pure compounds
- Technical information does not contain details of the classification of hazardous substances
- Manufacturers' information on the toxicological properties at workplaces and the nature and scale of workplace exposure is not generally available.
- Lack of pharmaceutical knowledge for interpretation of the available information (care facilities, surgeries)



Medicinal products containing potentially hazardous active agents are difficult to identify.

Knowledge required for safety-related information on medicines and associated activities:



And more besides.

© Trueeffelpix - Fotolia.com

BESI Project

(safety-relevant information on medicines and associated activities)

Bereitstellung von **s**icherheitsrelevanten **I**nformationen zu Arzneistoffen und damit verbundenen **T**ätigkeiten

Toxicological properties



Job-related exposure conditions

Antiinfectives pilot project:

- Gathering information
- Classification into categories of toxicity

Evaluation

Planning of protective measures

BESI: pilot project with antiinfectives

93 antiinfective lead substances (selection based mainly on drug prescription practice in Germany, 2010 report)

- Antibiotics
- Antimycotics
- Virostatic agents
- Antiseptic agents

BESI

Toxicological properties:

- Sensitising properties
- Carcinogenicity
- Mutagenicity
- Reproductive toxicity



© Brian Jackson-Fotolia.com

Classification into categories:

BESI category	Description
Sah, Sa, Sh, S	Sensitising substances
1	Very toxic/toxic substances in the form of substances with known CMR properties
2	Substances with suspected CMR properties
3	Substances without CMR properties, including irritant or corrosive substances without rationale for a higher classification

BESI: data sources (1)

- Safety data sheets (SDS) supplied by the European Directorate for the Quality of Medicines & HealthCare (EDQM)
- SDS issued by Sigma-Aldrich and other companies
- Switzerland's drug compendium (technical information)
- The Drug Information Portal of the German Bund (Federal Government) and the Laender (Federal States), Rote Liste (official German pharmaceutical catalogue)
- "Dailymed", U.S. National Library of Medicine
- TRGS (German Technical Rules for Hazardous Substances) 907: "List of sensitising agents and activities with sensitising agents"



© Gina Sanders-Fotolia.com

BESI: data sources (2)

- European public assessment reports published by the EMA (European Medicines Agency)
- Standard series of patch tests, German Contact Dermatitis Research Group (DKG)
- Information published by the International Agency for Research on Cancer (IARC)
- TOXNET databases
- "Mutschler Arzneimittelwirkungen" – textbook of pharmacology and toxicology
- Evaluation of reproductive toxicity risks by the Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy



© Gina Sanders-Fotolia.com



BESI: sensitising properties – criteria for classification



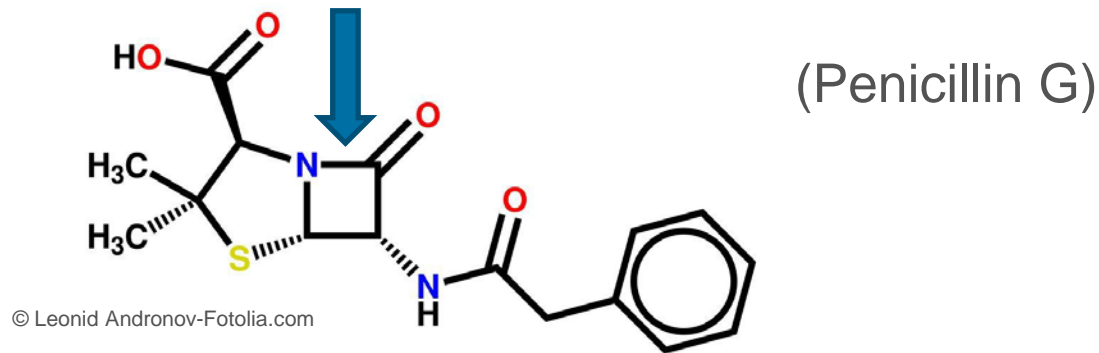
Ambrosia

- Definition: drug hypersensitivity reactions (skin, respiratory tract)
- Available data:
 - Hazard statements (H317, H334)
 - Positive test results (for example Guinea-Pig Maximisation Test (GPMT) or Local Lymph Node Assay (LLNA))
 - Standard series of patch tests, German Contact Dermatitis Research Group (DKG)
 - Frequency of possible side effects (frequently 1-10%; occasionally 0.1-1%) according to technical information
 - Mechanism of action

BESI: example of penicillin (H317/H334)

Mechanism of action:

Beta-lactam-structure



- Very reactive molecule, possible covalent binding to endogenous proteins after breaking of the beta-lactam ring → full antigen

BESI: evaluation of the sensitising properties (1)

Sensitising properties: 58 active substances

Amoxicillin (Sah)	Colistimethate (Sah)	Nystatin (Sh)
Ampicillin (Sah)	Doxycycline (Sah)	Ofloxacin (S)
Azithromycin (Sah)	Emtricitabine (S)	Oseltamivir (Sh)
Bacitracin (Sah)	Ertapenem (S)	Oxytetracycline (Sah)
Benzylpenicillin (Sah)	Erythromycin (Sah)	Pentamidine (Sh)
Cefaclor (Sah)	Fosfomycin (Sah)	Phenoxymethyl penicillin (Sah)
Cefadroxil (Sah)	Framycetin (Sh)	Piperacillin (Sah)
Cefazolin (Sah)	Fusidic acid (Sh)	Polyhexanide (Sh)
Cefixim (Sah)	Gentamicin (Sh)	Polymyxin B (Sah)
Cefotaxim (Sah)	Imipenem (Sah)	Povidone-iodine (Sh)
Cefpodoxim (Sah)	Kanamycin (Sh)	Ribavirin (Sh)
Ceftazidim (Sah)	Levofloxacin (Sah)	Roxithromycin (Sah)
Ceftriaxon (Sah)	Meropenem (Sa)	Sulfamethoxazole (Sah)
Cefuroxim (Sah)	Miconazole (Sh)	Sultamicillin (Sah)
Ciclopirox (Sah)	Minocycline (Sah)	Tetracycline (Sah)
Chloramphenicol (Sh)	Moxifloxacin (S)	Tigecycline (Sah)
Ciprofloxacin (Sh)	Neomycin (-sulphate) (Sh)	Tobramycin (Sh)
Clarithromycin (Sah)	Nitrofurantoin (Nitrofurazin) (Sh)	Trimethoprim (S)
Clindamycin (Sh)	Norfloracin (S)	Tyrothricin (Sah)
Clotrimazole (Sh)		

58 active substances

Categories:

Sa: Respiratory

Sh: Skin

Sah: Respiratory+skin

S: Sensitising, not specifiable

BESI: evaluation of the sensitising properties (2)

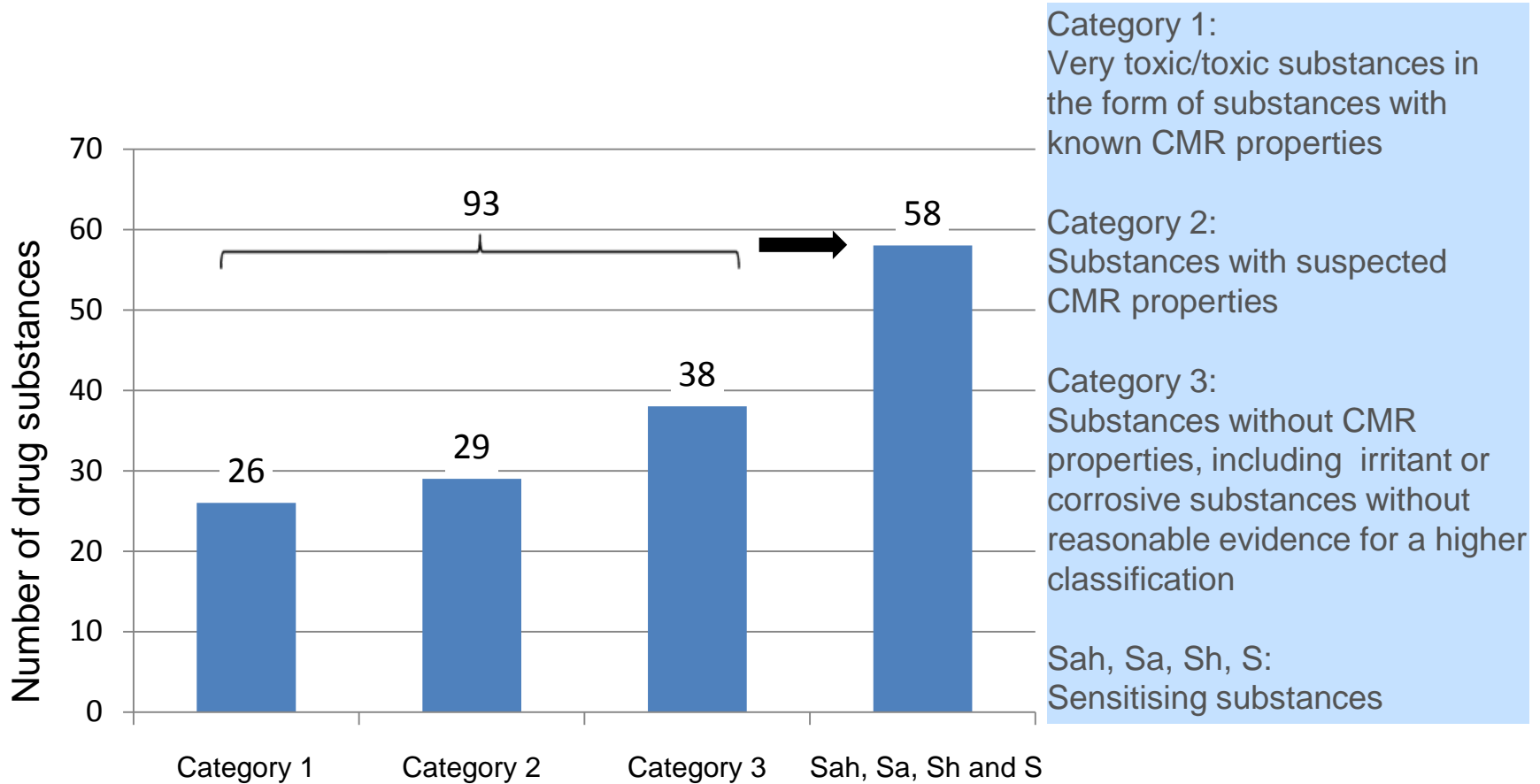
Drug classes/combinations	Classification
Penicillins	3, Sah*
Cephalosporins	3, Sah*
Tetracyclines	1, Sah*
Macrolides	3, Sah*
Sulfonamide combinations	2, S/Sah
Fluoroquinolones	2, S
Aminoglycosides	1, Sh*

Categories:

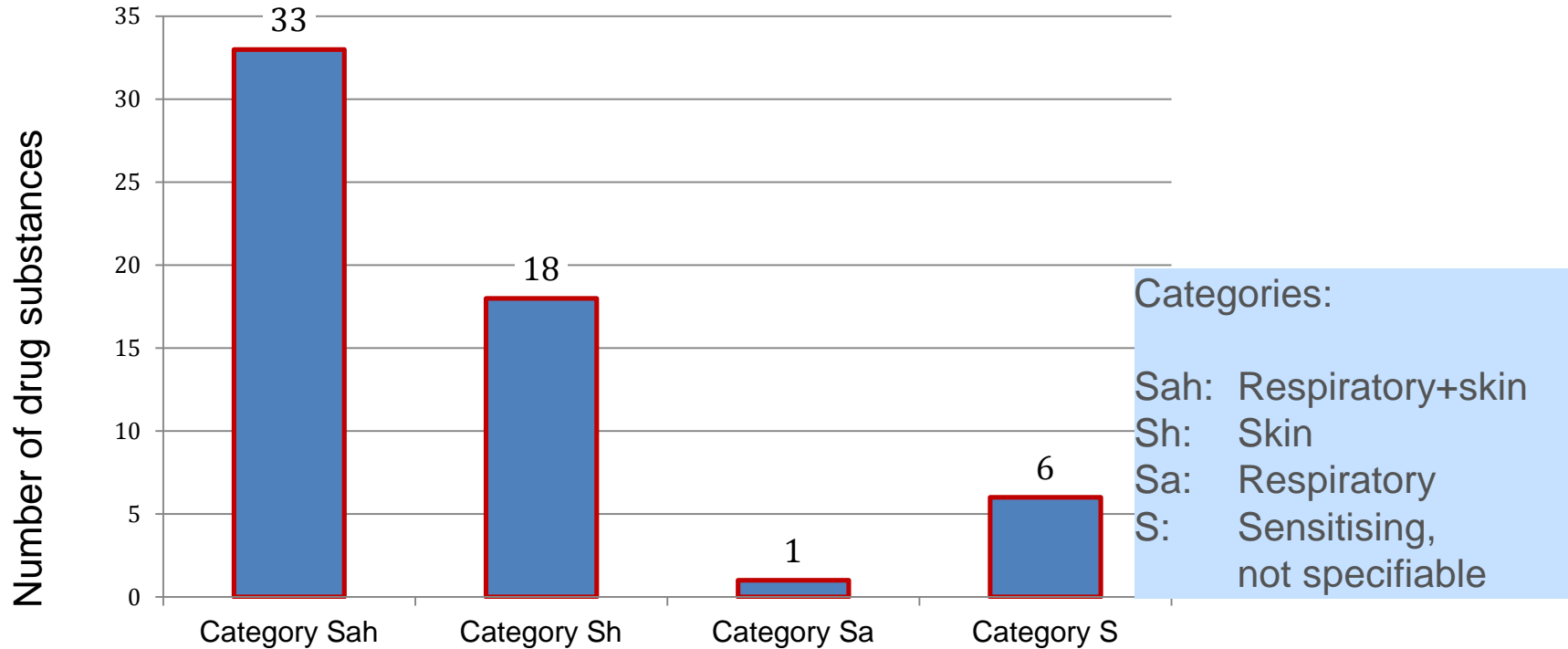
Sa: Respiratory
 Sh: Skin
 Sah: Respiratory+skin
 S: Sensitising,
 not specifiable

*Sah, Sh: Group classification was performed according to German Technical Rules for Hazardous Substances (TRGS) 907

BESI results: classification into categories



BESI results: distribution of sensitising properties



BESI: transferability to the situation of workers?

- Toxicological data used in the study generally derive from tests in which the **intake paths and the quantities** administered **are not generally comparable** with the exposure situation at workplaces.

Example: Imipenem/Cilastatin

Therapeutic intravenous administration

➡ Exposure of employees?

- Therapeutic application (antiinfectives): **higher** dose per exposure
- Occupational exposure: **lower** dose per exposure but possibly repeated exposure

➡ **How much is actually released at workplaces?**



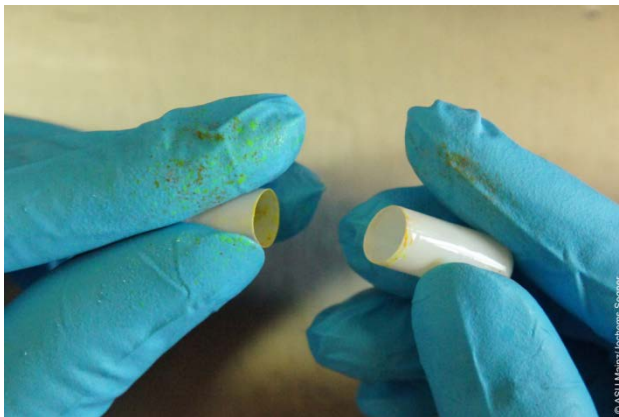
© jojje11-Fotolia.com

BESI: how much is actually released at workplaces?

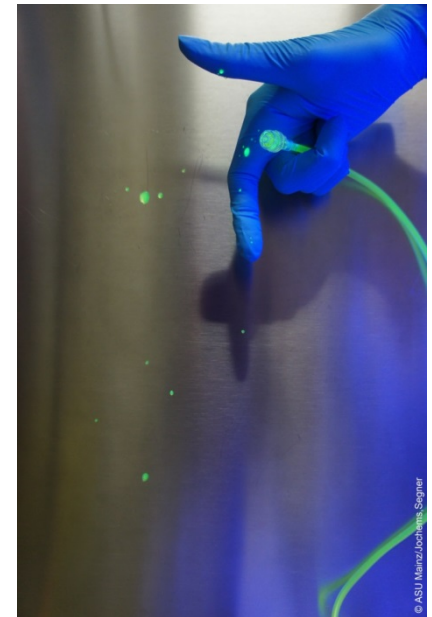
Exposure and contamination at workplaces:
studies with naproxen/fluorescein sodium acting as
tracer substances

Remove infusions cap

Opening of the capsule



Cleaning of the mortar



**Small quantities are sufficient to
cause possible allergic reactions.**

*With kind approval of the
Institute of Occupational, Social and Environmental Medicine
at Johannes Gutenberg University, Mainz*

Relevance for daily work: case studies concerning allergic contact sensitisation (1)

Review: Minciullo et al. (2013), Airborne contact dermatitis to drugs.

- Work activities:
 - Nurses are most affected
 - Pharmaceutical workers, pharmacists
 - Use of veterinary drugs: farmers, animal attendants, surgeons
- Pharmaceutical contact allergens:
 - Antibiotics, corticosteroids and immunosuppressive drugs, inhibitors of gastric secretion, analgesics, neurological drugs, antihypertensives, other molecules
- Affected body parts:
 - Exposed areas (face, neck, hands etc.)
 - Reactions on non-exposed areas (by particles trapped under clothing) have also been reported
 - Generalised reactions may occur due to inhalation or transcutaneous absorption

Relevance for daily work: case studies concerning allergic contact sensitisation (2)



Case study:

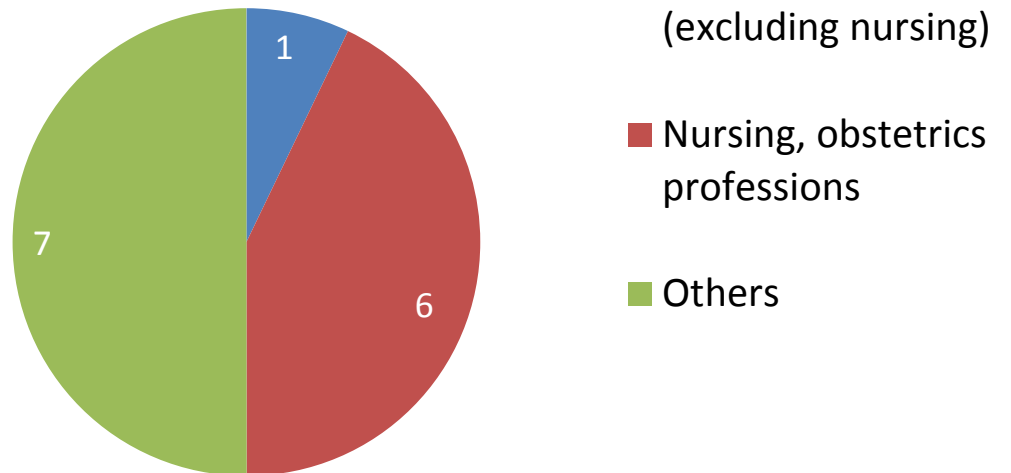
Landeck et al. (2011), Airborne contact dermatitis to tetrazepam in geriatric nurses – a report of 10 cases.

JEADV 2012, 26: 680-684.

"Work related skin changes after crushing tetrazepam, affecting the face and neck"

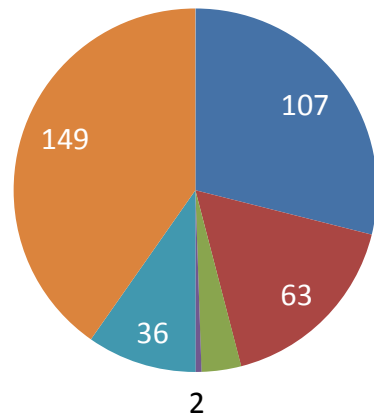
Relevance for daily work: Documented occupational allergic diseases in Germany (DGUV statistics 2005-2014) induced by drugs (1)

Allergic respiratory diseases (“BK 4301
Atemwegserkrankung allergisch”)
14 confirmed cases 2005-2014



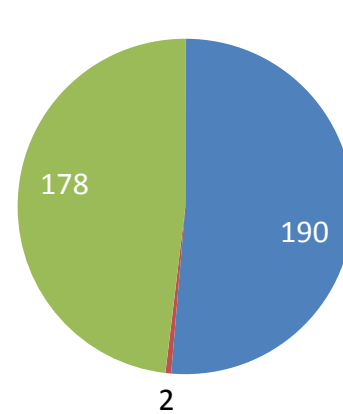
Relevance for daily work: Documented occupational allergic diseases in Germany (DGUV statistics 2005-2014) induced by drugs (2)

**Dermatitis
("BK 5101 Hautkrankheiten")
induced by drugs
370 confirmed cases**



- Medical professions (excluding nursing)
- Nursing, obstetrics professions
- Physicians (excluding nursing)
- Scientific nursing, obstetrics professions
- Care professions and related occupations
- Others

**Specification of dermatitis
192 confirmed cases caused by
allergy**



- Allergic contact dermatitis
- Allergic urticaria
- Others

Summary and conclusions (1)

- Millions of healthcare workers are exposed to potentially sensitising solid and liquid drugs (crushing of tablets, administration of infusions...)
- Risk assessment of medicinal products at the workplace is difficult
 - Medicinal products in the finished state are excluded from mandatory marking of hazardous substances
 - Generally, no manufacturers' information available on the toxicological properties of the substances used at work and the nature and scale of workplace exposure

The quality of manufacturers' information must be improved with respect to occupational safety and health.

Summary and conclusions (2)

BESI project results (Heinemann et al., 2015; www.bgw-online.de):

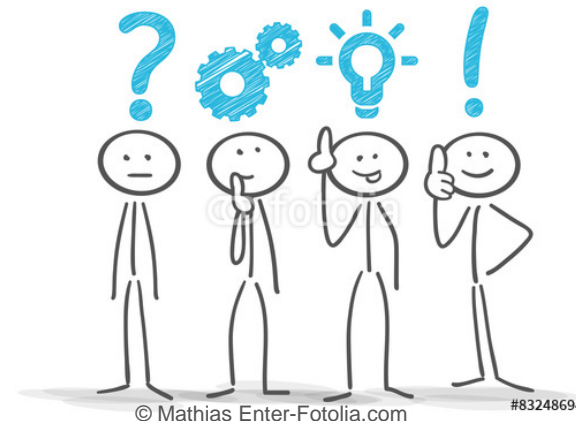
- More than 50% of the evaluated antiinfectiva (93) have sensitising properties
- Most of these are respiratory sensitisers
- For further evaluation, the actual intake pathways at work need to be considered



Summary and conclusions (3)

Required:

- **Minimum protection measures (such as gloves)**
- **Improved work organisation**
- **Better training for healthcare workers** (a highly topical subject: chemical-specific training in safe handling was ranked as lowest for aerosolised antibiotics in a NIOSH study of 12,028 healthcare workers (2014))
- **Raising awareness for sensitising drug substances**



Acknowledgements

- BGW: Professor Dr Udo Eickmann, Dr André Heinemann, Cologne
- Dr Lilla Landeck (hospital Klinikum Ernst von Bergmann, Potsdam)
- Professor Dr Stephan Letzel, Christoph Heynemann, Philipp Jochems, Dr Renate Kimbel, Dr Bernd Roßbach, Verena Segner (Institute of Occupational, Social and Environmental Medicine at Johannes Gutenberg-University, Mainz)
- Dr Angela Möller, Dr Eberhard Nies (IFA, Sankt Augustin)
- Dr Stephanie Padberg (Embryotox, Berlin)
- Stephanie Schneider (DGUV, Berlin)

Thank you for your attention!

Je vous remercie de votre attention!



Dr Sabine Werner
Institut für Arbeitsschutz der Deutschen Gesetzlichen
Unfallversicherung (IFA) (Institute for Occupational
Safety and Health of the German Social Accident
Insurance)

Fachbereich 1 - Informationstechnik,
Risikomanagement Referat Toxikologie der
Arbeitsstoffe (Toxicology of Industrial Chemicals)

Alte Heerstraße 111
53757 Sankt Augustin
Germany

Tel.: +49-(0)2241/231-2662
Fax: +49-(0)2241/231-2234
E-Mail: Sabine.Werner@dguv.de
URL: www.dguv.de/ifa

Literature

- Heinemann A, Werner S, Padberg S, Möller A, Heynemann C, Roßbach B, Hadtstein C, Nies E. Sicherheitsrelevante Informationen zu Arzneistoffen und damit verbundenen Tätigkeiten. Erste Teilergebnisse des BGW-Projektes BESI . Gefahrstoffe –Reinhaltung der Luft. 2015 Jan-Feb, 75: 23-31. http://www.dguv.de/medien/ifa/de/pub/grl/pdf/2015_001.pdf
- Landeck L, Skudilik C, John SM. Airborne contact dermatitis to tetrazepam in geriatric nurses – a report of 10 cases. JEADV 2012, 26, 680-684.
- Minciullo PL, Imbesi S, Tigano V, Gangemi S. Airborne contact dermatitis to drugs. Allergol Immunopathol (Madr). 2013 Mar-Apr; 41(2):121-6.
- Steege AL, Boiano JM, Sweeney MH. NIOSH health and safety practices survey of healthcare workers: training and awareness of employer safety procedures. 2014 Jun; 57(6) :640-52