

# Management of genotoxic impurities – a view from pharma industry

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UCB Biopharma

**NVT Spring Symposium : Genotoxic impurities in pharmaceutical products**

Utrecht 24 april 24



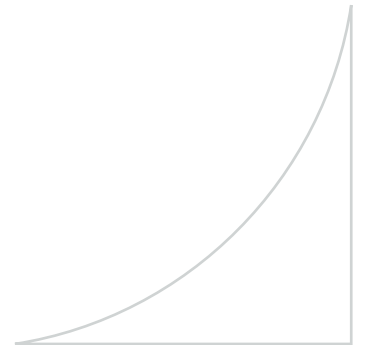
Inspired by **patients.**  
Driven by **science.**





# Agenda

- Introduction
- Hazard assessment
- Risk characterization & acceptable intakes
- Control strategies
- Case studies



# Introduction



Reactive chemicals, reagents, catalysts and solvents are commonly used in the synthesis of drug substances



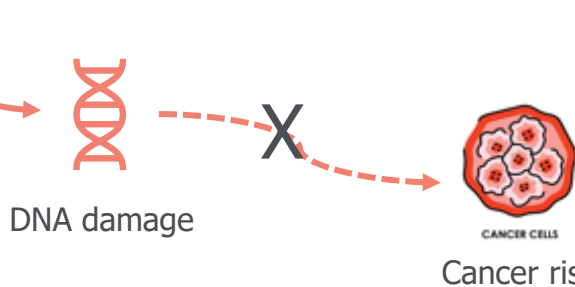
can appear as impurities in drug substance or drug product  
can include starting materials, reagents and intermediates



Reactive compound



API



## Regulatory framework

ICH Q3A - drug substances  
ICH Q3B - drug products

Guidance for qualification and control of impurities

ICH M7 – potential mutagenic (DNA-reactive) impurities

Specific guidance to limit cancer risk

# ICH M7 (R2) – Purpose & scope

## Focus

- substances that have a potential to directly cause DNA damage (mutagenic carcinogens)

## Aim

Provide a practical framework that can be applied to :

- identify
- categorize
- qualify
- control

potentially mutagenic impurities to limit the potential carcinogenic risk

Give guidance on:

- which impurities need to be considered
- how the assessment needs to be conducted
- when the assessment needs to be conducted
- the extend of the assessment to be conducted depending on the clinical phase
- the methodology to be used

## Outcome

- safety and risk management to establish mutagenic impurity limits that are expected to pose a negligible risk for patients



## Scope

- new drug substances and new drug products during their clinical development
- new marketing applications
- post-marketing if changes in manufacturing process result in new impurities or degradation products
- new chemical entities (not for : new biological entities, peptides, oligonucleotide, cancer products, excipients)

# Impurities assessment



## What

- impurity identification
- hazard assessment
- establishing safe limits
- risk characterization purge factor
- control measures

## When

- during drug development
- post-marketing

## Which

Actual and potential impurities that are likely to arise

- during the synthesis and storage of a new drug substance
- during manufacturing and storage of a new drug product
- actual degradation products when the levels exceed the identification thresholds outlined by ICH Q3A/Q3B

# Hazard assessment of mutagenic impurities

ICH  
M7

- initial toxicological assessment of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data
- computational toxicology assessment requires the use of 2 complementary (Q)SAR prediction methodologies; one expert rule-based & one statistical-based

at  
UCB



Derek Nexus – rule-based  
toxicophores matching alerts in the knowledge database



Leadscope – statistical knowledge-based  
publicly available bacterial mutagenicity data as well a proprietary  
data from corporate sponsors



Literature search



Expert review



Assessment report with classification

# Hazard assessment & classification

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- initial analysis of actual and potential impurities
- each impurity will be assigned to one of the five classes

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

define acceptable intake based on carcinogenic potency and linear extrapolation

\* Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations



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TTC-based acceptable intake

\* Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations

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5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

An appropriately conducted negative bacterial mutagenicity assay would overrule any structure-based concern

Of note: when levels of the impurity cannot be controlled at an appropriate acceptable limit, it can be tested in an in vivo gene mutation assay in order to understand the relevance of the bacterial mutagenicity assay result under in vivo conditions



\* Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations

# Hazard assessment & classification

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ICH Q3A/Q3B – Impurities in new drug substance/drug product

\* Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations

# Risk characterization - defining acceptable intakes

## The threshold of toxicological concern (TTC) concept

- define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity
- when adequate data to perform a compound-specific toxicological assessment are not available
- based on very conservative approach

- for mutagenic impurities in pharmaceuticals : acceptable intake of **1.5 µg/day**
  - corresponding to negligible risk  
(theoretical excess risk of cancer of 1 in 100000 over lifetime exposure)

Of note

The TTC approach is not applicable for high carcinogenic potency structural groups such as aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds

→ compound-specific assessment

# Risk characterization - Less-Than-Lifetime (LTL) exposures

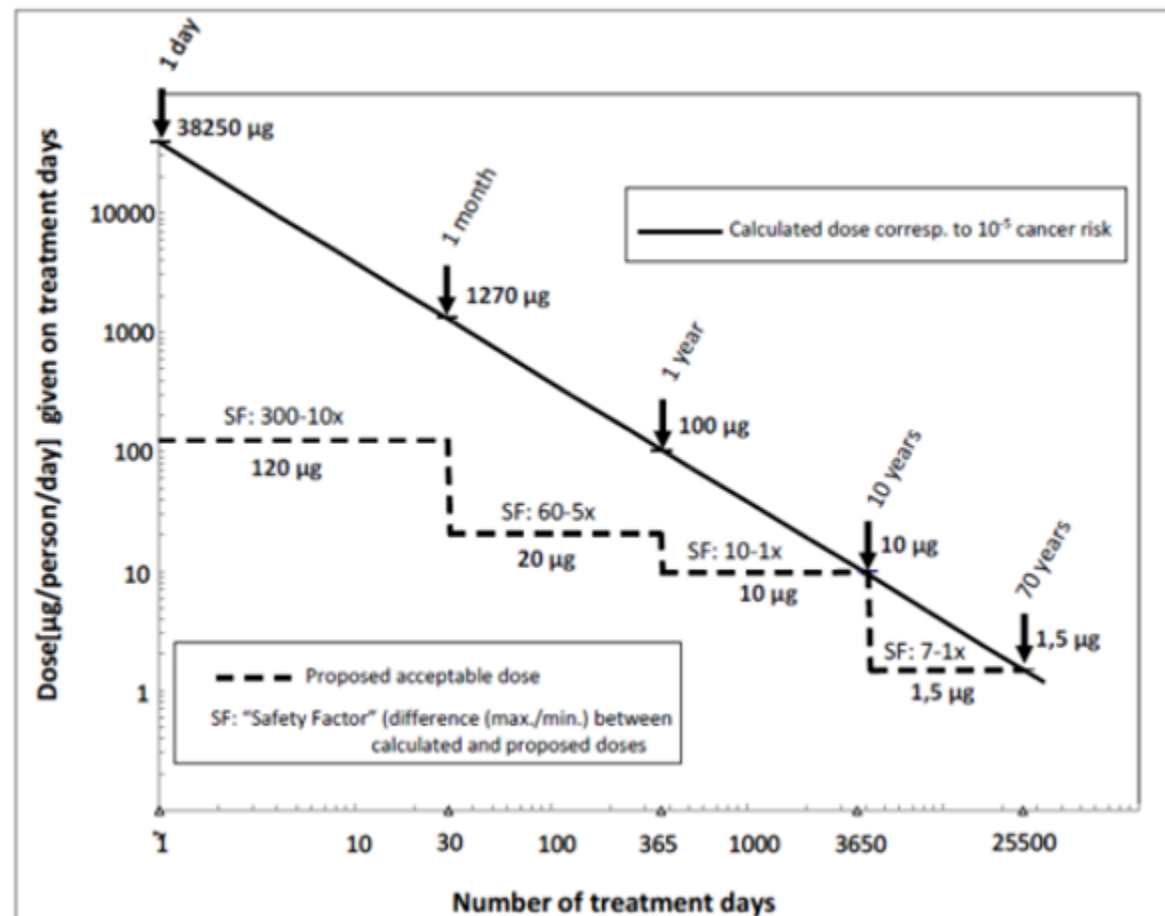
- can have higher acceptable intakes of impurities and still maintain comparable risk levels

Table 2 : Acceptable daily intakes for an individual impurity

Duration of treatment	≤1 month	>1 – 12 months	> 1 – 10 years	> 10 years to lifetime
Daily intake (µg/day)	120	20	10	1,5



Figure 1: Illustration of calculated daily dose of a mutagenic impurity corresponding to a theoretical 1:100,000 cancer risk as a function of duration of treatment in comparison to the acceptable intake levels as recommended in Section 7.3.



# Risk characterization - Multiple mutagenic impurities

- when there are  $\geq 3$  class 2 or class 3 impurities in the drug substance or the drug product, total daily intakes should be limited



Table 3 : Acceptable total daily intakes for multiple impurities

<b>Duration of treatment</b>	<b><math>\leq 1</math> month</b>	<b>&gt;1 – 12 months</b>	<b>&gt; 1 – 10 years</b>	<b>&gt; 10 years to lifetime</b>
Total daily intake ( $\mu\text{g}/\text{day}$ )	120	60	30	5

# Control strategies for process impurities

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Once acceptable intakes have been defined, it is important to develop a control strategy that assures that the level of this impurity in the drug substance and drug product is below the acceptable limit

## 4 options

1. control the impurity with a **specification for the API** (acceptance criterion  $\leq$  the acceptable limit)
2. control the impurity with a **specification for a starting material or intermediate** (acceptance criterion  $\leq$  the acceptable limit)
3. same as option 2 but acceptance criterion above acceptable limit of the impurity  
→ should be coupled with demonstrated **understanding of fate and purge** that assure the level in the drug substance is below the acceptable limit
4. relying on **process controls (fate and purge scientific knowledge)** to ensure the level of the impurity will be below the acceptable limit → no analytical testing required (no impurity specification)



- thorough understanding of chemistry associated with manufacturing process
- purge knowledge

# Control strategies for process impurities

Purge = the ability of the process to remove impurities

$$\text{purge ratio (PR)*factor} = \frac{\text{predicted purge factor}}{\text{required purge factor to reach TTC or acceptable limit}}$$

- theoretical



purge tool

 **Mirabilis**

Mirabilis provides an industry-standardised approach for calculating purge factors of potentially mutagenic impurities

OR

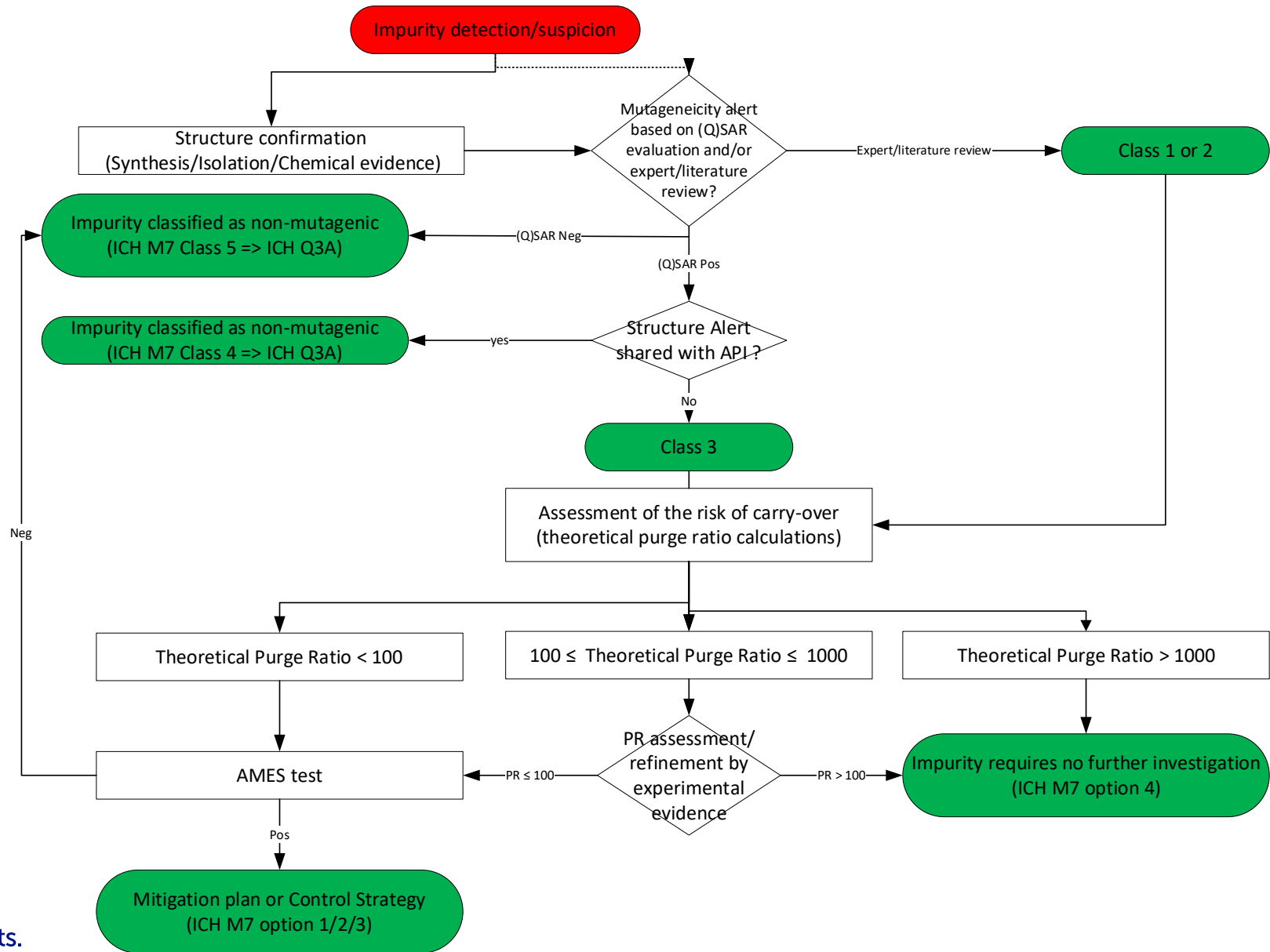
in-house expertise

- experimental



analytical testing (can be challenging)

# Overall risk assessment for process impurities at UCB



# Assessment of mutagenic impurities at UCB

**Case study 1 :** Change in synthetic route of Drug A → Compound X is a new intermediate in the synthesis of Drug A

→ daily dose 400 mg → TTC = 3,75 ppm



Positive in silico assessment (structural alert identified by Derek) → class 3  
→ in vitro mutagenicity test → positive → class 2 → controlled at TTC



Later, an in vivo micronucleus test was performed in the frame of Reach  
→ negative → class 5 → controlled according to ICHQ3A and B (much higher level allowed)

an impurity can be tested in an in vivo genotoxicity assay in order to understand the relevance of the bacterial mutagenicity assay result under in vivo conditions



# Assessment of mutagenic impurities at UCB – some case studies

## Case study 2 : Marketed compound – change in synthetic route

→ daily dose 200 mg → TTC = 7,5 ppm



Glyoxilic acid is a starting material in step 1 of the synthesis route (unspecified impurity - potentially present)

- presents a mutagenicity alert in Leadscope
- in a series of in vitro and in vivo genotoxic studies, all studies provided negative results
- not mutagenic → class 5 → treat as normal impurity
- high theoretical purging factor → impurity controlled



Glyoxal is an impurity in glyoxylic acid starting material (unspecified impurity - potentially present)

- presents a mutagenicity alert in Derek and Leadscope
- described in public databases and in literature → mutagenic based several in vitro and in vivo test results
- class 2 → control according to ICH M7
- very high experimental purging (>6000-fold) demonstrated with spiking experiments → residual levels are < 4 ppm at early step of synthesis → further purged in downstream synthesis process → controlled

# Assessment of mutagenic impurities at UCB – some case studies

## Case study 2 : Marketed compound – change in synthetic route

→ daily dose 200 mg → TTC = 7,5 ppm



Valeraldehyde dimer is a process impurity formed in step 1 of the synthesis route (specified impurity)

- presents a mutagenicity alert in Derek and is negative or indeterminate in Leadscope
- no information on genotoxicity could be found in public databases for this specific compound - mutagenicity has been reported for alkenals but not for alkyl-alkenals
- GLP Ames test performed → not mutagenic → class 5 → treat as normal impurity
- very high theoretical purging factor → cleared in downstream process → controlled



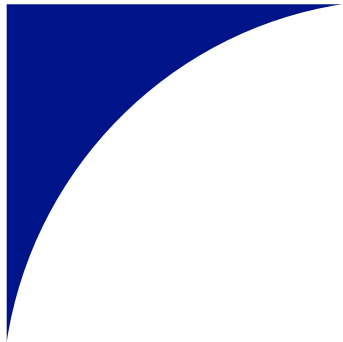
Hydroxyfuranone is a synthesis intermediate and specified impurity in step 1 of the synthesis route

- presents mutagenicity alerts in Derek and Leadscope
- GLP Ames test performed – positive in strains Salm typh TA100 and E coli WP2uvrA → mutagenic
- class 2 → control according to ICH M7
- process change introduced in step 2 to purge the impurity < TTC → controlled

# In summary

- The management of mutagenic impurities in pharmaceuticals products requires a continuous evaluation throughout drug development
- A close collaboration between safety evaluation, process chemistry and analytical development departments is needed in order to control (mutagenic) impurities to acceptable limits and minimize the risk for patients





## Thank you to my UCB colleagues !

Pascale Jacques – Chemical & Environmental Safety (now Material Safety)

Georges Assaf – Chemistry and Process R&D

Nicolas Barbarin – Analytical Sciences



**Thank you**  
**Questions ?**

