

农药原药中毒性杂质评价与 控制策略的探讨

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报告著作权归原作者，仅供“论坛名称”参会代表查阅



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- ① 原药杂质研究的必要性
- ② 杂质的来源和类型
- ③ 新农药与非专利农药杂质控制策略的差异性
- ④ 杂质的控制策略
- ⑤ 案例分析



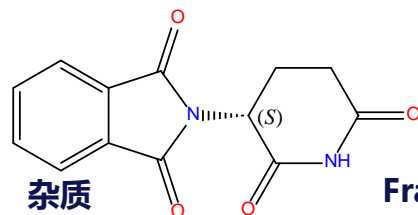
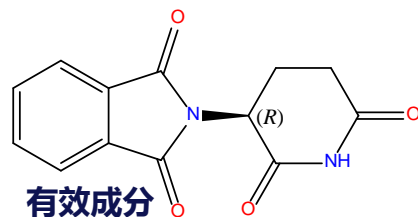
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原药杂质研究的必要性-历史事件

医药: 沙利度胺(反应停)

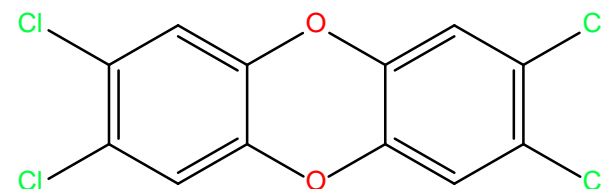
- 具有镇静催眠的药效, 尤其对孕反抑制明显
- 上市后导致新生儿畸形: “海豹肢畸形”
- **杂质来源**: 有效成分为光学异构体, R构型安全, S构型(即杂质)有致畸性, 且两种构型可在体内转化



Frances Kelsey
FDA评审员

农药: 橙剂

- 由2,4-D和2,4,5-T等比例混合而成的除草剂, 在越战中用于去除可供藏身的丛林树叶
- 造成越南的新生儿畸形, 美国退伍军人患癌率激增
- **杂质来源**: 在原药生产过程中, 极易生成一类致癌物二噁英(Dioxin)杂质



2,3,7,8-TCDD

各国均对原药杂质均设定了严苛的监管要求

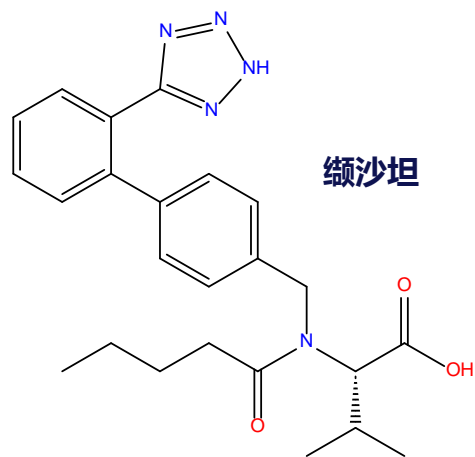
研究杂质的生成和安全性, 对原药中的杂质进行严格的控制, 以满足法规要求和质量标准

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原药杂质研究的必要性-对合规性的影响

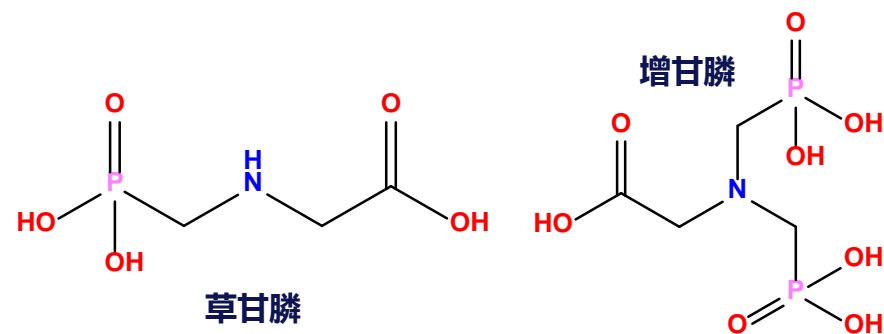
医药：缬沙坦亚硝胺杂质事件

- 2018年监管部门在缬沙坦原药中发现了**亚硝胺**杂质
- 多国对涉事来源的药品进行了评估和召回，并引发集体诉讼和颁布进口禁令
- 相关企业暂停了生产，直至2021年才整改完成



农药：2023年欧盟草甘膦新增杂质

- 欧盟草甘膦再评审过程分两阶段新增了多个相关杂质
- **增甘膦**杂质因遗传毒性研究不充分拟被列为相关杂质，并被设定了严格的限量要求
- 基于甘氨酸生产工艺的草甘膦原药出口欧盟可能会受限，但预计全球范围内的影响在短期内将会较为有限





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杂质的来源



杂质的类型

显著杂质

原药中含量超过1 g/kg (即超过0.1%)的杂质

相关杂质

- 由于杂质的健康毒理、生态毒理和环境行为等因素导致其在原药中的存在是不可接受
- 影响稳定性（如水）[FAO/WHO]
- 影响产品性能（如不溶物）[FAO/WHO]
- 非保密信息

非相关杂质

- 不属于相关杂质的其他杂质
- 保密信息

毒理批次

- 能够反映最坏情况下原药毒性情况
- 杂质的含量应尽可能接近拟制定的规格
- 在某些需要重点明确杂质对原药整体影响的毒理节点中，也可通过添加(**spike**)杂质的方式制备杂质含量超过规格样品来用于毒理试验中

问题1：所有需要评估的杂质都是显著杂质么？

问题2：如何判断一个杂质是否是相关杂质？



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新农药与非专利农药杂质控制策略的差异性

相同点：

符合法规要求（**规则**），对杂质的生成原因和安全性进行研究

差异性：

• 新农药：

- **核心：构建壁垒**
- 研究深度侧重在原创性研究
- 明确规格、相关杂质和非相关杂质

• 非专利农药：

- **核心：挑战壁垒**
- 研究深度侧重在一致性研究
- 工艺匹配与优化、非相关杂质的限度挑战

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杂质的控制策略:

a) 分析杂质的生成原因并进行控制

原料控制：

- 避免使用不符合要求的中间体、溶剂(参考ICH Q3C)等

生产工艺控制：

- 基于已有的工艺，推断可能的副反应及产生的杂质
- 判断混入最终原药中的可能性与应对策略
- 尤其是对于高关注杂质(如亚硝胺，二噁英)
- 分析方法的开发与检测
- 清除与净化或工艺优化的必要性

稳定性检测与降解产物分析：

- 检测降解产物和对生成机理分析

2024
CHEMICAL
REVIEWS

Mechanisms of Chemical Carcinogenicity and Mutagenicity: A Review
with Implications for Predictive Toxicology

Romualdo Benigni* and Cecilia Bossa

Istituto Superiore di Sanita', Environment and Health Department, Viale Regina Elena, 299 00161 Rome, Italy

REVIEW

pubs.acs.org/CR

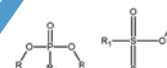
Acylating, direct acting agents

SA_1: Acyl halides

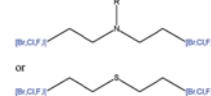


Alkylating, direct acting agents

SA_2: alkyl (C<5) or benzyl ester of
sulfonic or phosphonic acid



SA_5: S or N mustard



SA_7: Epoxides and aziridines



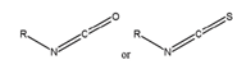
SA_9: Alkyl nitrite



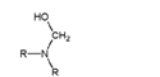
SA_11: Simple aldehyde



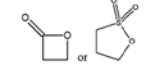
SA_15: isocyanate and isothiocyanate groups



SA_3: N-methylol derivatives



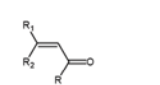
SA_6: Propiolactones or propiolactones



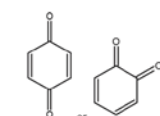
SA_8: Aliphatic halogens



SA_10: α, β unsaturated carbonyls

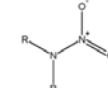


SA_12: Quinones

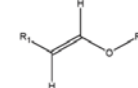


Alkylating, indirect acting agents

SA_23: aliphatic N-nitro group



SA_24: α, β unsaturated aliphatic alkoxy group

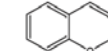


Intercalating and DNA-adducts forming, indirect acting agents

SA_18: Polycyclic Aromatic Hydrocarbons

Three or more fused rings, not heteroaromatic

SA_30: Coumarins and Furocoumarins



Aminoaryl DNA-adducts forming, indirect acting agents

SA_25: aromatic nitroso group



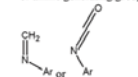
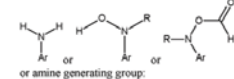
SA_26: aromatic ring N-oxide



SA_27: Nitro-aromatic



SA_28: primary aromatic amine, hydroxyl amine and
its derived esters



SA_28bis: Aromatic mono- and dialkylamine



SA_28ter: aromatic N-acyl amine



SA_29: Aromatic diazo



杂质的控制策略:

b) 明确杂质的安全性

- 杂质安全性评估的目的：
 - 对杂质进行系统的毒理学评估
 - 基于杂质的毒理学数据制定其在原药中可接受限值
 - 制定相关杂质和非相关杂质
- 关键的毒理学数据：
 - **遗传毒性**
 - 急性毒性、短期毒性、或更高阶的试验
- 评价方法：
 - (Q)SAR和毒理试验 → 杂质毒理学评估
 - 风险评估 → 杂质限度制定



杂质的控制策略:

b) 明确杂质的安全性：为什么在原药中需要重点关注遗传毒性杂质(GTIs)?



Paracelsus

毒理学之父
“剂量决定毒性”

From the [Wikimedia Commons](#)

但对于**遗传毒性物质 (genotoxicity impurities, GTIs)**来说，只要其存在暴露，对人体就有可能引起DNA损伤，进而增加了癌症诱发概率。

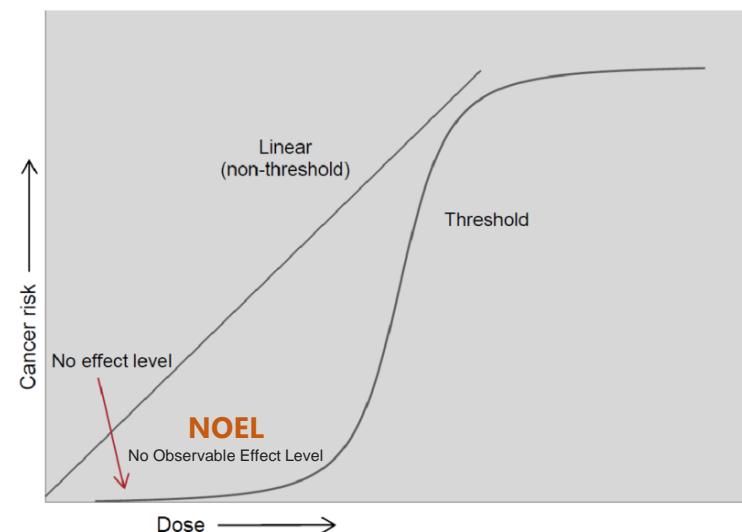
遗传毒性



癌症发生



遗传毒性致癌物 (Genotoxic carcinogens): are chemicals that exert carcinogenicity via the induction of mutations. Owing to their DNA interaction properties, there is thought to be no safe exposure threshold or dose (无安全暴露阈值或剂量, non-threshold). Genotoxic carcinogens are regulated under the **assumption** that they pose a cancer risk for humans, even at very low doses.



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杂质的控制策略:

b) 明确杂质的安全性：对原药中杂质进行遗传毒性评估的方法

- ***in silico***: (Q)SAR, read-across, etc.
- ***in vitro*** 细菌回复突变试验: OECD TG 471 (**Ames test**)
- ***in vitro*** 哺乳动物细胞基因突变: OECD TG 476, etc.
- ***in vitro*** 哺乳动物细胞染色体损伤: OECD TG 473, 487, etc.
- ***in vivo*** 基于体细胞: OECD TG 474, 486, 488, 489, pig a, etc.
- ***in vivo*** 基于生殖细胞: OECD TG 483, 488, etc.

杂质的控制策略:

b) 明确杂质的安全性：(Q)SAR模型是什么？

- **(Q)SAR** = (Quantitative) Structure-Activity Relationship (定量)结构-效应关系
 - **原理**：通过模型建立分子结构与生物活性/毒性(e.g., mutagenicity, carcinogenicity, developmental and reproductive toxicity)之间的联系
 - **基本假设**: 相似结构的化合物具有相似的性质
化合物的潜在**毒性**能够通过**分子结构**来做出判断
- 通过(Q)SAR模型的建立能够保障预测结果的一致性与无偏性
Fill data gaps when empirical evidence is unavailable or inadequate

$$\text{(Q)SAR} \quad f(\text{分子结构}) = \frac{\text{生物活性/毒性}}$$

分子结构

生物活性/毒性

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杂质的控制策略:

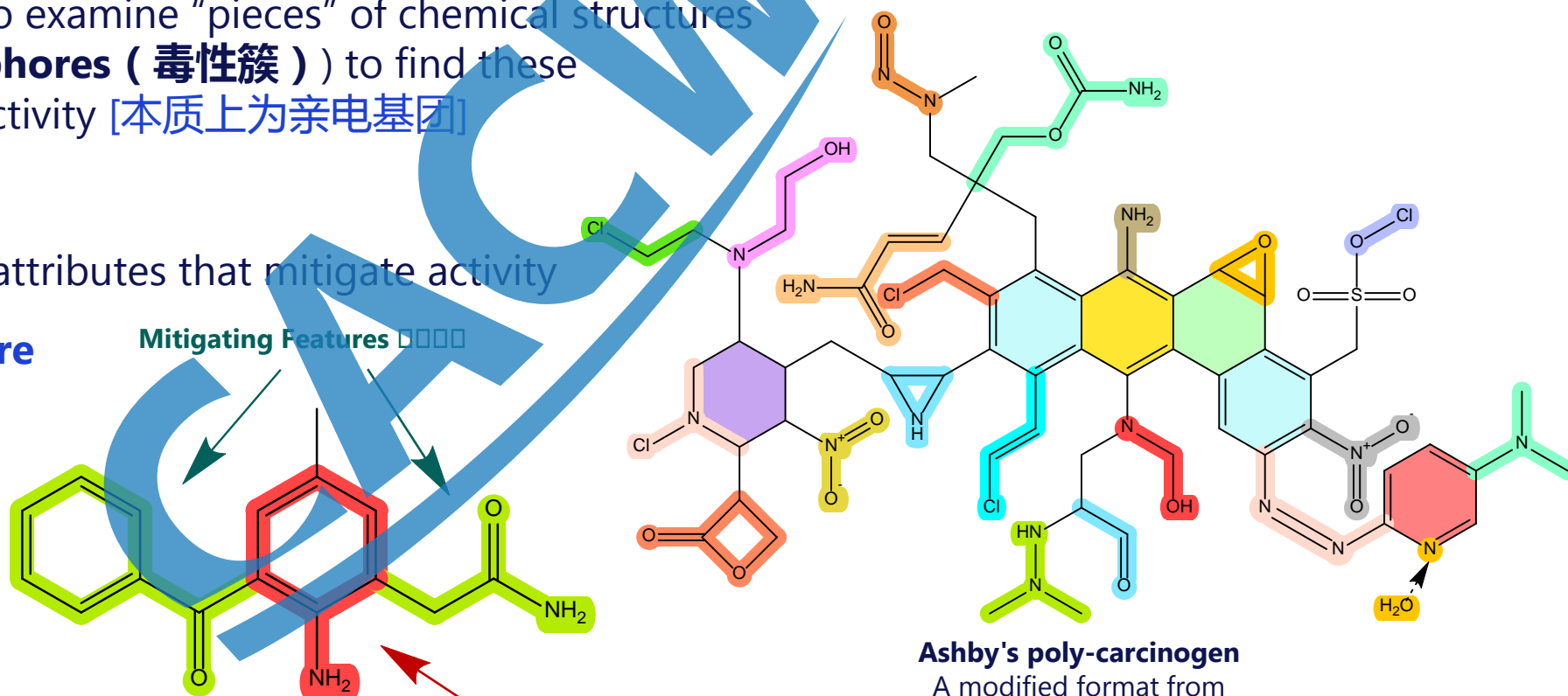
b) 明确杂质的安全性：(Q)SAR模型如何解释毒性作用机制？

- Model learns from the results of actual laboratory testing
 - Use a computer to examine “pieces” of chemical structures (or called **toxicophores (毒性簇)**) to find these associated with activity [本质上为亲电基团]

➡ Structural alert

- Can also identify attributes that mitigate activity

➡ Mitigating Feature



This [example](#) is from Dr. Kruhlak, 2021, US FDA

Structural Alert

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杂质的控制策略:

b) 明确杂质的安全性：(Q)SAR的统计学模型和规则模型

- **统计学模型Statistical-based models** (or called **mathematical-based models**)
 - e.g., partial least squares regression analysis (PLS), support vector machines (SVM), neural networks (ANN/SNN/DNN).
 - 无偏性，灵敏度较高
 - 低可解释性
 - **定性结果** (e.g., Ames positive) Or **定量结果** (e.g., rat LD₅₀, fish LC₅₀)
- **专家知识规则模型Expert rule-based models** (or called **knowledge-based models**)
 - Human expert (e.g., toxicologists) knowledge driven approach
 - 存在经验偏差，灵敏度较低
 - 高可解释性，可提供作用机制信息及相关的研究出处
 - 通常仅只有**定性结果** (e.g., Ames positive)

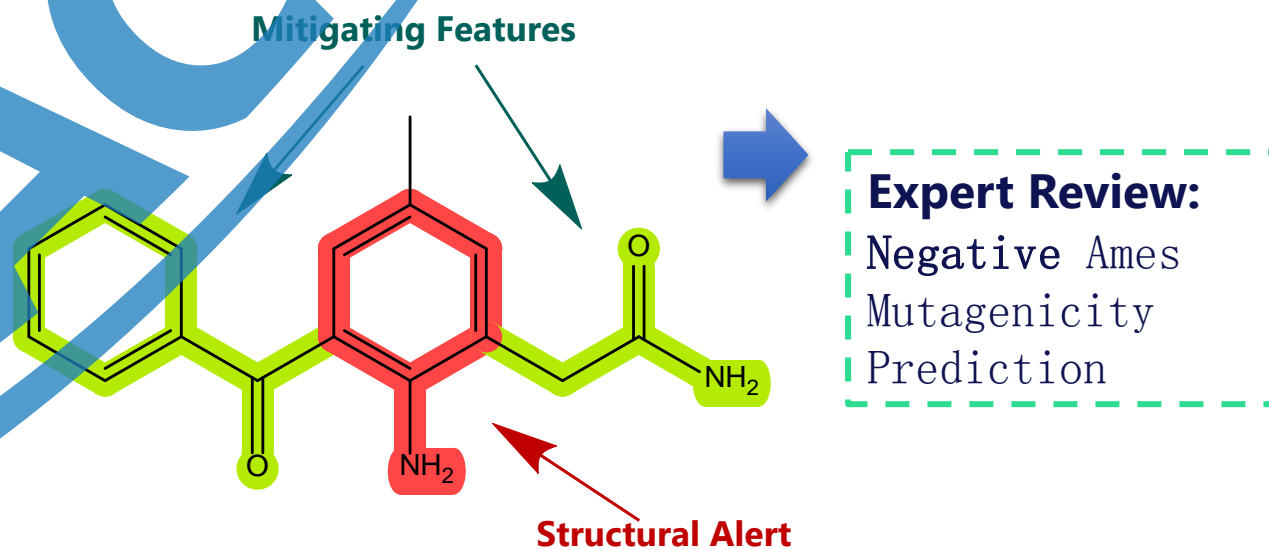
杂质的控制策略:

b) 明确杂质的安全性：(Q)SAR预测的结果需要进行系统的专家评估

ICH M7 (Pharmaceuticals)

"...the use of expert knowledge in order to provide additional supportive evidence on relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion"

- 对化合物的分子结构中出现的结构警报进行识别与解释
- 如果可能的话，综合分析可能的毒性作用机制 [如，一级苯胺(primary aromatic amines)会被体内代谢为亲电基团(nitrenium species)]
- 评估训练集中的已知毒性化合物，进一步分析毒性增强和毒性减弱基团[即充分评估模型输出结果]
- 同时在整个评估过程中需要考虑未被模型使用的其他相似化合物的数据 [即充分评估除训练集以外的其他类似化合物的结果]



This [example](#) is from Dr. Kruhlak, 2021, US FDA

杂质的控制策略:

b) 明确杂质的安全性：为杂质设定合理可接受限度的策略总结

Circumstances	How to establish an acceptable upper limit concentration
Impurities are rat/human metabolites (代谢物) produced in significant levels (10%)	The toxicity of this impurity could be considered to be assessed in toxicity studies with the a.i. (e.g., SANCO/10597/2003, APVMA, ICH Q3A)
Impurities are structurally similar to a.i. (有效成分)/ metabolite (代谢物)/ relevant impurities (相关杂质)/ other structural analogues (结构类似物) with available data	(Q)SAR, read-across, literature search and expert review to derivate Health-Based Exposure Limits (HBELs) for conducting risk assessment of impurities OR use same control strategies for impurities and their similar compounds.
Impurities belong to chemical classes of well-known toxicological concern (高关注毒性化合物), such as nitrosamines, dioxins, etc.	Acceptable maximum concentration should be considered on a case-by-case evaluation according to present knowledge (e.g., WHO TEFs for dioxins, below 1 mg/kg for total N-nitrosamines.).
Impurities have been classified for adverse toxicological properties (e.g., intermediates 中间体)	<ul style="list-style-type: none">The generic concentration limits (0.1% or 1%) applicable for these impurities (e.g., GHS classification concentration limit)Derivate Health-Based Exposure Limits (HBELs)
Certain solvents (溶剂 e.g., dichloromethane, toluene)	Derivate permitted daily exposures (PDEs) in accordance with pharmaceuticals guidelines (e.g., ICH Q3C) for conducting risk assessment of these solvents.
Positive predictive values of impurities from (Q)SAR results (最常见的情况)	<ul style="list-style-type: none">The generic concentration limits (0.1% or 1%) applicable for impurities which could be classified for adverse toxicological properties (e.g., GHS classification concentration limit)Calculate the suitable TTC values for conducting risk assessment of impurities.

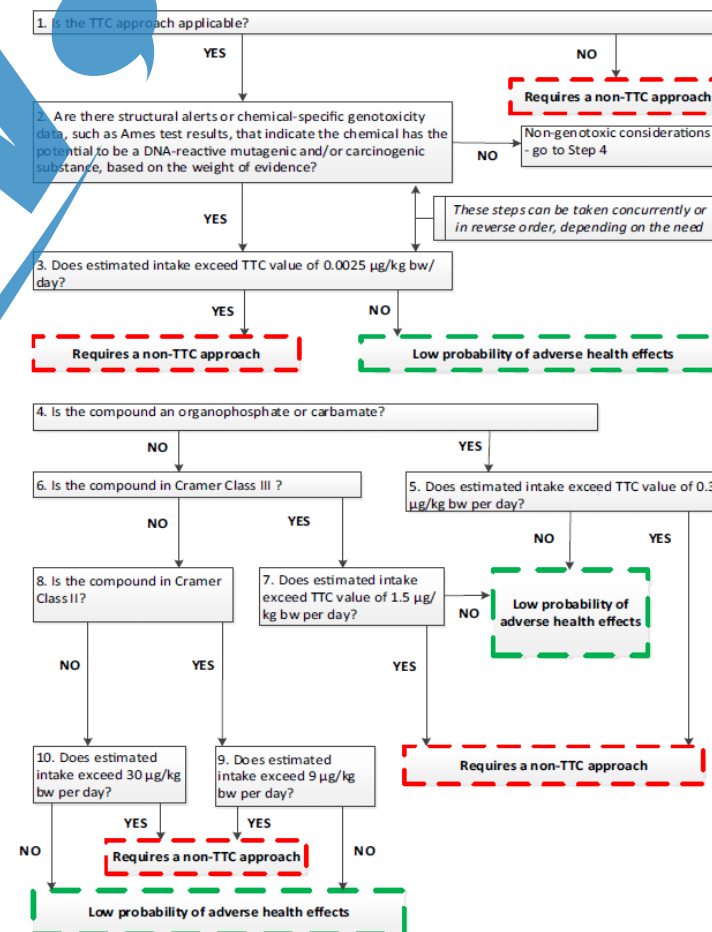
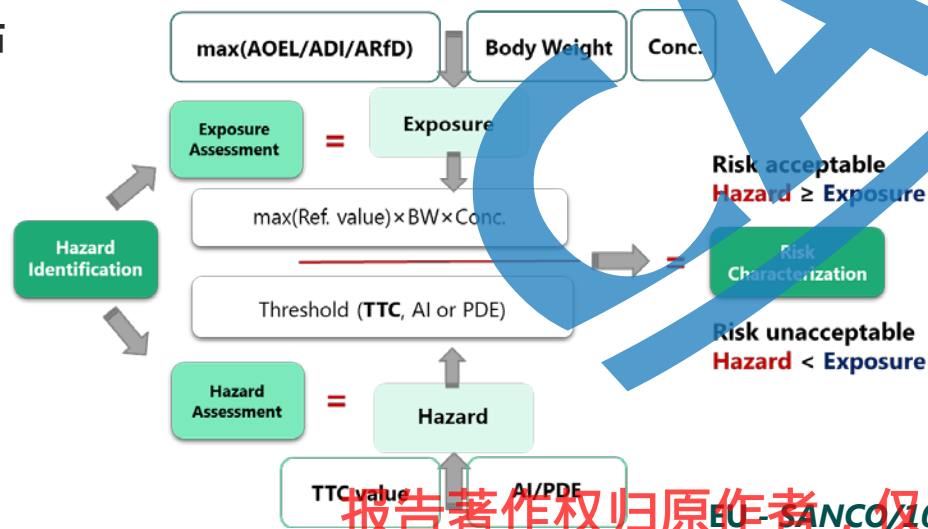
杂质的控制策略:

b) 明确杂质的安全性：为遗传毒性杂质设置合理可接受限度

How to identify **DNA-reactive mutagens/carcinogens**:
Experimental values, **(Q)SAR**, and/or read-across

Classification	TTC values in µg/person/day	TTC values in µg/kg bw/day
Potential DNA-reactive mutagens/carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1,800	30

风险评估



杂质的控制策略:

c) 匹配拟进入国家的法规要求: 以欧盟为例

• 新农药登记与再评审(EU No 283/2013) :

3.4.2013 EN Official Journal of the European Union L 93/1

II (Non-legislative acts)

REGULATIONS

COMMISSION REGULATION (EU) No 283/2013 of 1 March 2013

setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (⁽¹⁾), and in particular Article 78(1)(b) thereof,

Whereas:

(1) In accordance with Article 8(4) of Regulation (EC) No 1107/2009, Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances (⁽²⁾) was adopted. It contains the requirements for the dossiers to be submitted for the approval of active substances, as set out in Annex II to Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market (⁽³⁾).

(5) A reasonable period should be allowed to elapse before the modified data requirements become applicable in order to permit applicants to prepare themselves to meet those requirements.

(6) In order to permit Member States and the interested parties to prepare themselves to meet the new requirements, it is appropriate to lay down transitional measures concerning data submitted for applications for the approval, renewal of approval or amendment to the conditions of approval of active substances and data submitted for applications for authorisation, renewal of authorisation and amendment to the authorisation of plant protection products.

(7) These transitional measures are without prejudice to Article 80 of Regulation (EC) No 1107/2009.

(8) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on the Food Chain and Animal Health and neither the European Parliament nor the Council has opposed them.

HAS ADOPTED THIS REGULATION:

• 等同登记-非专利农药(SANCO/10597/2003) :



EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Safety of the Food Chain
Chemicals, contaminants, pesticides

SANCO/10597/2003 –rev. 10.1
13 July 2012

GUIDANCE DOCUMENT ON THE ASSESSMENT OF THE EQUIVALENCE OF TECHNICAL MATERIALS OF SUBSTANCES REGULATED UNDER Regulation (EC) No 1107/2009

This document has been conceived as a working document of the Commission Services, which was elaborated in co-operation with the Member States. It does not intend to produce legally binding effects and by its nature does not prejudice any measure taken by a Member State within the implementation prerogatives under Regulation (EC) No 1107/2009, nor any case law developed with regard to this provision. This document also does not preclude the possibility that the European Court of Justice may give one or another provision direct effect in Member States.

Revision history	
When	What
Rev. 10.1 of 13.07.2012	Update of Appendix 1 containing the flow chart and time table on the procedure for the assessment of the equivalence of new sources of technical materials according to Article 38 of Regulation (EC) No 1107/2009.

杂质的控制策略:

c) 匹配拟进入国家的法规要求: 各国等同登记的法规要求



EU - SANCO/10597/2003

Human health Toxicity *"Ideally, (Q)SARs which are used for toxicological reasoning in the context of this document would be validated at the EU level and well documented especially in terms of their applicability domain, and (in the case of quantitative relationships) the statistical method used for their development along with the associated statistical uncertainty"*

Ecotoxicity (especially for impurity presenting at > 1%) *"...In particular, the use of SAR or QSAR approaches is limited by the lower availability of reliable models for the whole spectrum of taxonomic groups occurring in the environment"*



Netherlands, etc. For the Tier II toxicological assessment should follow the requirements according to GD SANCO/10597/2003, and there is no specific QSAR model required. Applicant may have conducted SAR analysis on the impurity using a recognized system (e.g., Derek Nexus, OECD QSAR Toolbox)



France, etc. For the Tier II toxicological assessment should follow the requirements according to GD SANCO/10597/2003, and in order to increase the sensitivity and specificity of the prediction, two independent and reliable (Q)SAR models (**statistic-based** and **knowledge-based models**) should be provided.

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(Q)SAR models may be used to provide information on impurities of unknown toxicity. They must be scientifically valid and in order to maximize the sensitivity and specificity of the prediction, at least two independent (Q)SAR models, where possible, (e.g., based on different training sets and/or algorithms such as **knowledge based** and **statistical-based models**) should be applied (EFSA, 2016).

Applicant should provide the **calculation** of worst-case-possible contribution by an impurity to the toxic hazards of the a.i. This calculations are based on known concentration of a.i. and impurity, and the toxicity (LD₅₀, ADI, BMD, etc.) of the impurity and TC/TK by using the dose-additivity model.

EFSA (European Food Safety Authority). 2016. Guidance on the establishment of the residue definition for dietary risk assessment. EFSA Journal, 14(12): e04549.
<https://doi.org/10.2903/j.efsa.2016.4549>

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The **genotoxic potential** of the impurity should be assessed using *in silico* (computation) models. **Two** types of *in silico* (computational) methodologies must be used:

1. An **expert rule-based model**, and
2. A **statistically based model**

If any of the *in silico* analyses are positive, then it is necessary to conduct genotoxicity testing on the active ingredient.

However, if one impurity is the rat metabolite produced in a significant level, the toxicity of this impurity could be considered to be assessed in toxicity studies with the active ingredient.



Australian Government
Australian Pesticides and
Veterinary Medicines Authority

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- Three studies of structural-activity relationship should be present by using **three specialist systems**, or one study using **three specialist systems**.

An example for three specialist systems:

1. Derek Nexus
 2. OECD QSAR Toolbox
 3. VEGA HUB
- For the active ingredient and its impurities, the structure-activity relationship studies or the supporting data must cover the endpoints evaluation of a technical product is require, in accordance with current legislation (e.g., mutagenicity, carcinogenicity, developmental/reproductive toxicity).
 - In addition, it is emphasized that when a particular expert system is used, analysis must be performed for **ALL** endpoints in it available, necessary to evaluate a technical material.

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- The QSAR predicted results could be used for the calculation of worst-case-possible contribution by an impurity to the toxic hazards of the a.i. in accordance with the FAO/WHO specification for chemical pesticides.
- This calculations are based on known concentration of a.i. and impurity, and the toxicity (LD_{50} , ADI, BMD, etc.) of the impurity and TC/TK by using the dose-additivity model.
- **Rat LD_{50}** is one of toxicity data which are easy to obtain, this LD_{50} value of impurity can be taken from recognized toxicological databases (e.g., [ChemIDplus](#)) or predicted by QSAR model (e.g., [T.E.S.T.](#))
- Other endpoints such as mutagenicity, teratogenicity, and carcinogenicity may be provided if COFEPRIS further requires



目录

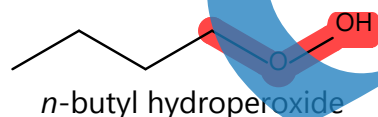
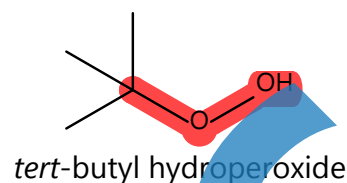
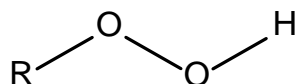
- 1 原药杂质研究的必要性
- 2 杂质的来源和类型
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- 4 杂质的控制策略
- 5 案例分析

明确杂质毒性产生机制

结构警报能够反映作用机制，需要系统的运用这些机制信息去分析杂质中所含有的结构警报是否会对杂质的安全性产生整体性影响

Structural Alert: Hydroperoxide 过氧化氢化物

R1 = H, C (alkyl), *C(R2)(R3)O
R2, R3 = any except
heteroatoms or double bonds
(Derek)

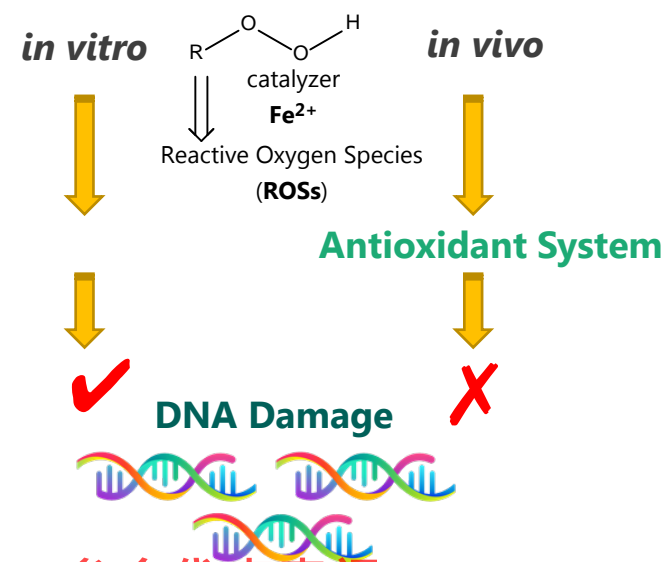


hydrogen peroxide

in vitro genotoxicity:
Positive

***in vivo* genotoxicity:**
Negative

Mechanism of Action



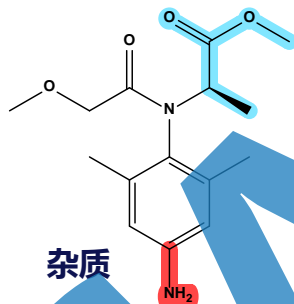
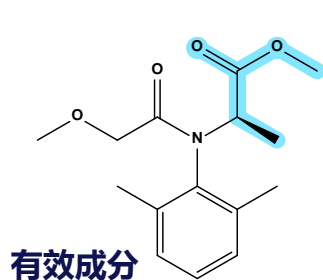
案例分析2 – 立体异构杂质的毒理学评估

难点

1. (Q)SAR模型不适用，并不能很好的区分立体异构的结构特征所带来的毒性差异
2. 制备纯化的立体异构体杂质难度大

应对策略

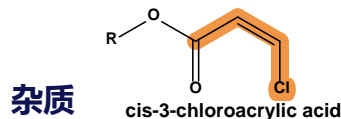
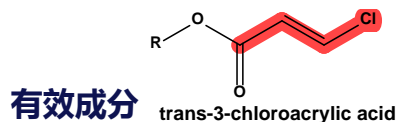
1. 明确杂质的毒性是否是由立体异构的结构特征所引起



3. 寻找同类立体异构化合物活性和毒性的规律

- L型活性**大**但毒性**小**，R型活性**小**但毒性**大**？
- L型活性**大**且毒性**大**，R型活性**小**且毒性**小**？
- 推断这一类化合物的特征来用于杂质的评估

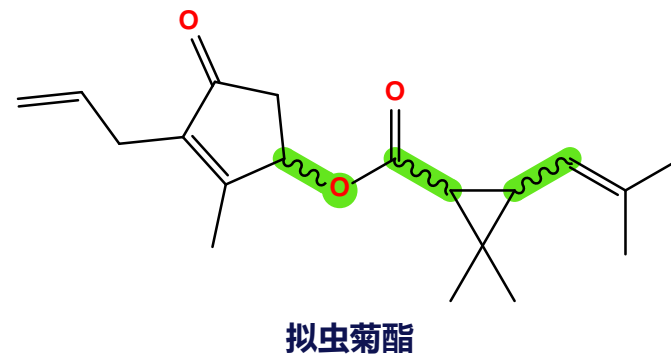
2. 能否找到能反映立体异构毒性特征的其他化合物、代谢物



Bridging



Metabolized



案例分析3 – 欧盟草甘膦再评审新增相关杂质的确定

最新欧盟草甘膦再评审相关杂质的设定

活性物质

- 草甘膦 (Glyphosate) ≥ 950 g/kg

相关杂质限量

- 草甘膦-N-亚硝基单钠盐 (NNG) < 1 mg/kg

- 甲醛 (formaldehyde) < 1 g/kg

- 三乙胺 (triethylamine) ≤ 2 g/kg 2021年拟新增

- 甲酸 (formic acid) ≤ 4 g/kg

- 增甘膦 (glyphosine) ≤ 3 g/kg 2023年拟新增



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案例分析3 – 欧盟草甘膦再评审新增相关杂质的确定

增甘膦相关杂质的设定原因与不合理之处

The presence of impurities in the material manufactured in production facilities (sources) can be influenced by the manufacturing process. The technical material from several sources of glyphosate manufactured by **members of the GRG** contained levels of the impurity (N,N-bis-phosphonomethylglycine, also known as 'glyphosine') below the limit of quantification (LOQ) i.e. present at levels less than 0.1 % in the final manufactured material. However, the issue is considered not finalised by EFSA given that a common reference specification for **all sources** was proposed by the GRG and since the presence of the impurity cannot be excluded, even if at very low levels.

It must also be underlined that glyphosine has not been confirmed to have clastogenic properties. Rather, based on the available studies carried out on glyphosine, a clastogenic potential cannot be excluded. Two in vitro tests investigating clastogenicity were carried out on glyphosine and were submitted and evaluated: the *in vitro* micronucleus test was negative, whereas the *in vitro* chromosome aberration study was positive.

Importantly, glyphosine was present in the batches of glyphosate tested in two in vivo micronucleus tests (an appropriate test to investigate clastogenicity) at levels of ~10 g/kg and of ~21 g/kg, respectively. Results of both in vivo micronucleus tests were negative, i.e. there was no evidence of clastogenicity.

EFSA noted in its Conclusion that the AGG disagrees with the conclusion that the issue could not be finalised and "*considers the genotoxic potential not to be of toxicological concern at the level of the proposed reference specification, since the impurity was present at a 7-fold higher level than that proposed for the reference specification in one in vivo micronucleus test performed with glyphosate*". The AGG proposed a level of 3 g/kg in the reference specification.

Given that the impurity has been tested twice *in vivo* at levels exceeding up to seven-fold the proposed limit and that both tests showed no indications of clastogenic potential, and given that there are mixed findings from the *in vitro* studies, the limit proposed by the AGG of 3 g/kg of glyphosine in the technical material as manufactured is considered to be sufficiently protective. Therefore, based on the information available the impurity is considered toxicologically relevant and a maximum level of 3 g/kg for glyphosine will be set in the approval.

Finally, since the impurity profile is dependent on the manufacturing process, including the starting materials used, applicants for product authorisation may also consider changing the production process or starting materials to produce glyphosate that does not contain glyphosine.

GRG成员生产的样品无增甘膦杂质（可能与IDA工艺有关），但在GRG提供的所有来源草甘膦原药中无法排除这一杂质

增甘膦在体外微核试验为阴性，在体外染色体畸变为阳性
增甘膦的致染色体断裂性 (Clastogenicity) 需要重点关注

用含增甘膦含量1%和2.1%的草甘膦原药（即可认为毒理批）开展了两组体内微核试验，结果为阴性，可初步排除相关原药的致染色体断裂性

可能考虑到遗传毒性通常无毒性阈值以及检测灵敏度，欧盟在测试样品规格浓度的基础上增加了7倍的安全系数(?未给出充分的依据)，并确定增甘膦为相关杂质，限量要求为0.3%

欧盟拟建议草甘膦制剂产品生产中尽量不要使用含增甘膦的草甘膦原药 (??????????)

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1. 杂质研究首要目的是要弄清杂质的生成机理，减少杂质的生成，最终能够提高原药质量
2. 注重农药法规规则的合理运用：构建壁垒 vs 挑战壁垒
3. 杂质的安全性评估和限度制定需要充分的遵循科学性和保守性，并综合的运用各种评估方法

致谢和参考文献

风险评估团队

农用化学品部

黄超

(eco)toxicity, e-fate,
exposure model, *in silico*



郭杰

toxicity, chemistry,
exposure model, *in silico*



张校铭

chemistry,
exposure model



胡伟

(eco)toxicity,
exposure model, *in silico*



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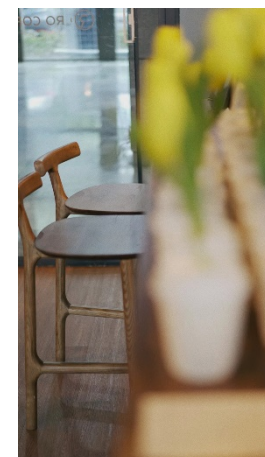
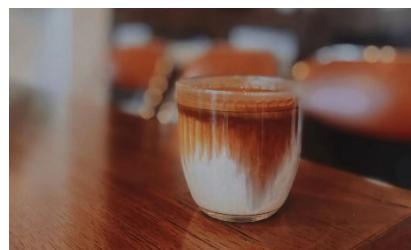
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