

外源有害物在生物体内生物学过程

梁俊平

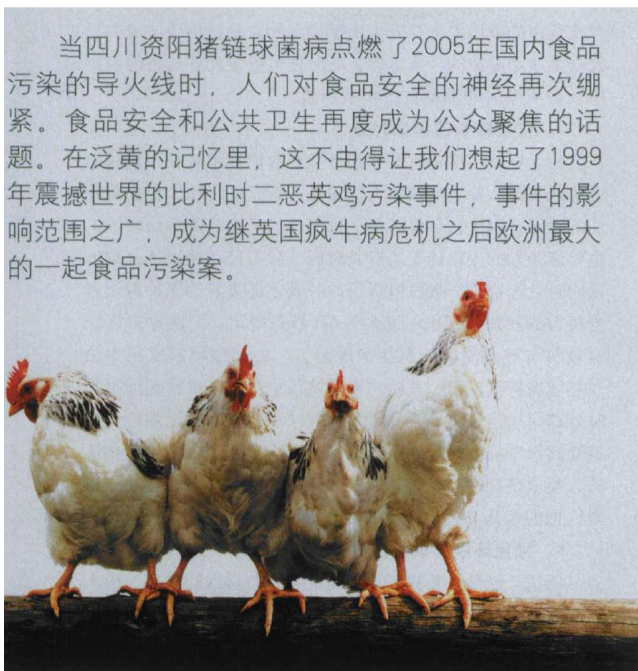
水产动物营养与饲料团队

2016-11-26

二噁英

公认的极毒，强致
癌物，有**世纪之毒**
之称。

- 目前为止，尚没有针对性的解毒药物，也没有促进其排泄的有效手段。



1999年比利时 二噁英 鸡污染事件

1999 Belgian dioxin
chicken pollution affair

文 / Seuly

当四川资阳猪链球菌病点燃了2005年国内食品污染的导火线时，人们对食品安全的神经再次绷紧。食品安全和公共卫生再度成为公众聚焦的话题。在泛黄的记忆里，这不由得让我们想起了1999年震撼世界的比利时二恶英鸡污染事件，事件的影响范围之广，成为继英国疯牛病危机之后欧洲最大的一起食品污染案。

二恶英鸡污染事件起因是饲料，最终 导致比利时内阁集体辞职

事端起于比利时一家叫维克斯特粉料生产厂，而问题出在饲料上。半个世纪以来，欧洲各国普遍在家禽和牲畜饲料中添加一种动物粉料，其主要原料是各种动物的骨头、皮、脂肪和下水。这种动物粉料含有禽畜生长所必需的蛋白质，使用添加这种粉料的混合饲料后，禽畜6周内就能从45克长到2.5公斤，上市周期大大缩短。这对饲养者来说自然很有吸引力。

1999年1月18日，维克斯特（Verkest）一辆装载动物油脂的油罐车遭受工业用油的严重污染。据调查，该厂有8吨粉料掺进了被二恶英严重污染了的工业用油。但在顾客需求和巨大利润的驱使下，1月19日至26日，维克斯特继续把被污染的动物油脂供应给9家比利时饲料生产厂，法国2家、荷兰和德国各1家饲料工厂也进口了维克斯特厂的粉料。这13家饲料厂又把污染了的饲料卖给了数以千计的饲养场。

二恶英污染就这样无声息地传播开了。

事态浮出水面是在1月底。比利时一家叫得伯让班德（de brabander）的养鸡户首先注意到他们的肉鸡生长异常，蛋鸡下蛋减少，因而向保险公司提出补偿要求。3月18日，保险公司将得伯让班德公司所购入的1月份生产的动物饲料样本送到实验室化验，结果发现鸡脂肪中二恶英的含量超最高允许量的140倍。比利时司法部门在对维克斯特厂调查时就发现了很多假发票。在比利时，由于饲料行业偷税漏税行为广泛存在，无法确定维克斯特厂是否仅将粉料卖给了这13家饲料厂，而这些饲料厂又究竟把饲料卖给了多少家农场。这是个难题，给控制二恶英污染制造了很大麻烦。

正式证实鸡肉被二恶英污染是4月26日。但5月12日，比利时政府卫生部长说他才知道这件事。即使如此，在后来的半个月里，政府仍没作出任何正式反应。

5月27日，在得知弗拉芒地区的一名记者对此事已有报道后，比利时政府卫生部长才作了一个简短的新闻

大闸蟹检出“二噁英”还能放心吃吗？

“现在正是吃大闸蟹的季节，美味的蟹膏蟹黄总是让人欲罢不能。不过，近日，香港特区食品安全中心通报，来自江苏两家养殖场的大闸蟹被检出致癌物二噁英含量超标。这一消息迅速在国内引起轰动，吃货们最忧心忡忡。二噁英是什么？大闸蟹中为何会出现二噁英？还能放心吃吗？”



通报指出，消费者如果摄入过量二噁英，可引起痤疮、皮肤出疹及变色等皮肤病，以及体毛过多等问题。国际癌症研究机构已把二噁英列为一类致癌物；长期摄入二噁英会牵涉到免疫系统、生殖功能、内分泌系统及发育中神经系统的损害。

而且，二噁英对生长发育的影响最为敏感，它会干扰儿童的内分泌，所以，婴幼儿面临的风险最大。

二噁英是如何产生的？

二噁英，大闸蟹生活在水里，还会吃点泥巴，自然也难免避免地会存在二噁英。

还能吃放心吃吗？

对于吃货来说，最关心的还是它是否

个安全线的意思是，即使你偶尔超过这个量也不会有危险，只有终生每个月都超过这个量才会有害。

即使我们按照此次检测出的最高量（40.3皮克毒性当量）来计算，一个体重60公斤的普通人，大约每个月要吃14只螃蟹（每只四两重计）才可能超过这个安全线。就算是二噁英类物质暴露量比较高的人，也需要每月吃三只才会超出安全线。

对于绝大多数吃货来说，吃螃蟹的季节，还是很容易超过这个量的。但是，螃蟹毕竟也是应季食品，一年里也就这么几个月能够吃到，绝大部分人不可能终生每个月都能够吃到这么多大闸蟹。所以，倒也不用担心会有危害。很多人可能担心，不是说几乎所有食物都可能含有二噁英吗，如果加上其他食物会不会有害？

香港曾经做过一个涵盖所有饮食数据的总膳食研究，结果显示，香港地区摄入量一般和摄入量高的人们每月从食物中摄入二噁英和二噁英样多氯联苯的分量分别为每公斤体重21.92皮克毒性当量和59.65皮克毒性当量，绝大多数人都是低于前面提到的安全线的。虽然这个数据并不能完全代表我们的情况，但是整体差异应该不会



大闸蟹门市显得冷清

2016年11月1日，香港特区食品安全中心官网通报显示，9月下旬，该中心在市场上抽查共12斤的大闸蟹样本，发现其中两个样本的二噁英含量超标，超标样本来自江苏省两个水产养殖场。蟹商生意额减少逾90%！

可能是饲料或环境被污染

专家表示，正常情况下，蓄意添加二噁英是不可能的；最可能是饲料被污染了，还可能是养殖环境被污染了，都可能导致检测结果超标。”

饲料与养殖水产品安全



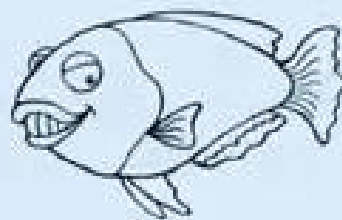
活饵料、下杂鱼、原料

病原
腐败有害物质
原料中有害物质
N、P污染 (3倍)



人工配合饲料

原料中有害物质
不当饲料添加剂
抗生素、激素 (?)
药物 (?)

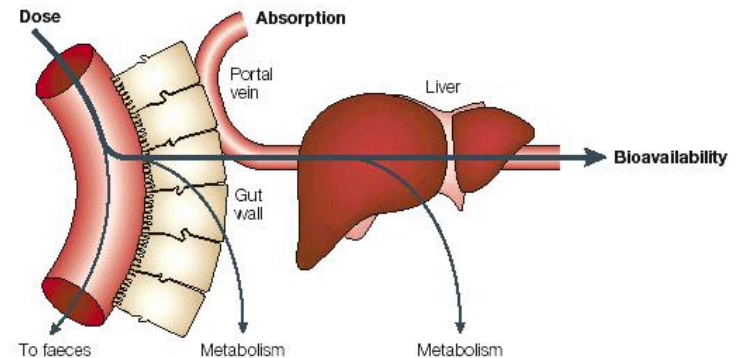


养殖水产品安全

外源有害物在生物体内如何代谢？

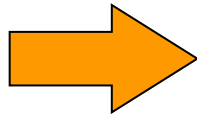
外源性化学毒物侵入机体后，有些是以其原形发挥毒性作用，大多数则在酶的作用下，改变了分子结构，导致增强或减弱原有的毒性。

毒物在体内发生的一系列生物转化过程即毒物的代谢过程。



ADME

Toxicant

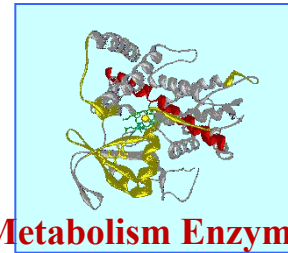


Absorption (A)

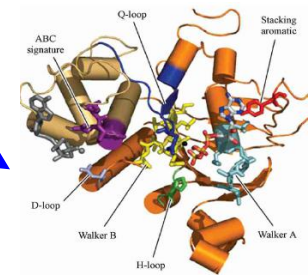
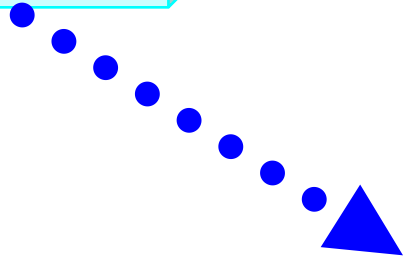
Distribution (D)

Metabolism (M)

Elimination (E)



Metabolism Enzymes



ABC (ATP-binding cassette) transporters

毒物代谢过程通常分为三个阶段:

第一阶段反应：是在酶的作用下**改变了**毒物分子的**功能基团**。

“I相反应” 或 “官能团反应”

第二阶段反应：是毒物或其代谢物同内源性小分子化合物**结合**。**“II相反应” 又称 “结合反应”**

第三阶段反应：是毒物或其代谢物外排过程。

“III相反应”

1. I 相反应及其代谢酶研究进展

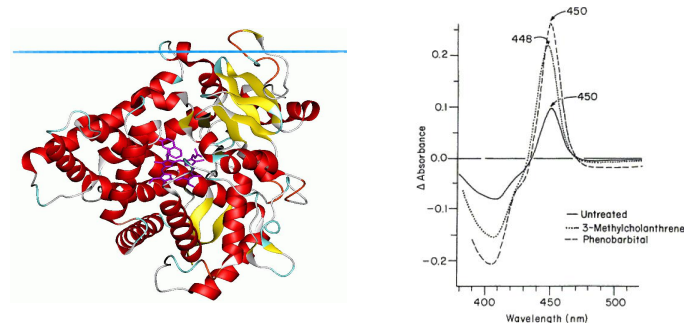
体内各种酶对毒物分子进行的官能团化反应，主要发生在毒物分子的官能团上，或分子结构中活性较高、位阻较小的部位，引入新的官能团及改变原有的官能团，包括氧化反应、还原反应、脱卤素反应和水解反应等。通过上述反应，向毒物（药物）母体分子引入某种极性基团（如羟基、羧基、氨基或巯等），改变毒物的结构，增加毒物母体分子的极性或水溶性，使脂溶性毒物转变为水溶性化合物。

表 2-3 一相药物代谢酶催化的内源性代谢

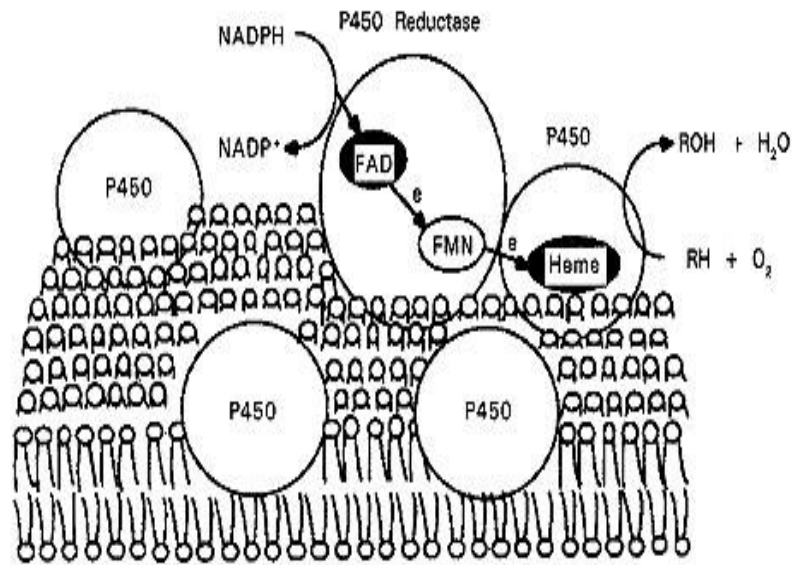
酶	内源性底物
混合功能氧化酶	甾体、固醇、甲状腺激素、脂肪酸、前列腺素、 V_D 、白三烯
单胺氧化酶	单胺神经递质
二胺氧化酶	组胺、腐胺、尸胺
黄嘌呤氧化酶	黄嘌呤
羟化甾体氧化还原酶	甾体
乙酰胆碱酯酶	乙酰胆碱
还原酶	甾类

细胞色素P450是I相反应的主要代谢酶，它通过催化底物的加氧或脱氢反应，使得底物具有亲水性，从而加速其代谢。

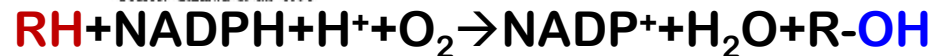
细胞色素 P450 酶系 (cytochrome P450 monooxygenases, CYP, 简称P450) 又称微粒体多功能氧化酶 (microsomal multisubstrate mixed function monooxygenase, MFO)、细胞色素P450 单加氧酶系、血红素硫蛋白等，是广泛分布于生物有机体中的一类代谢酶系 (冷欣夫, 2001)，是一簇结构、性质相似而又有差异，由超基因家族编码的含血红素和硫羟基的结合蛋白，因其与CO 结合形成的复合物在波长450nm 处有最大特征吸收峰而得名。



P450酶不仅可以代谢诸多外源物质（如药物、毒物等），还参与生物体内源物质（如激素、脂肪酸等）的代谢，在生物体中起着十分重要的作用。



Source: Ohtkawa *et al.* 1998



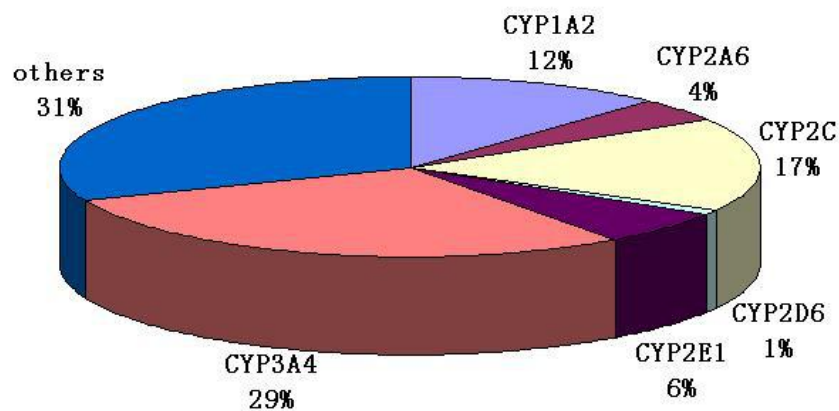
P450家族的主要成员

Famils	Sub-families
CYP1	A1,A2,B1
CYP2	A6,A13,B6,C8,C9,C18,C19,D6,E1,F1,J2,R1,S1
CYP3	A4,A5,A7,A43
CYP4	A11,B1,F2,F3,F8,F12,V2
CYP5-CYP20	CYP5 (A1) - CYP7 (A1,B1) - CYP8 (A1,B1) - CYP11 (A1,B1,B2) - CYP17 (A1) - CYP19 (A1) - CYP20 (A1)
CYP21-CYP51	CYP21 (A2) - CYP24 (A1) - CYP26 (A1,B1) - CYP27 (A1,B1) - CYP39 (A1) - CYP46 (A1) - CYP51 (A1)

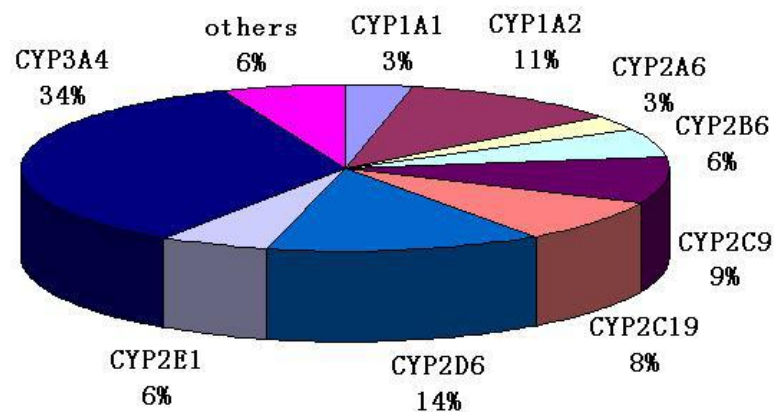
CYP1, CYP2, CYP3, CYP4 和 CYP7 被认为在肝和肝外代谢外源性化学物质和药物的消除方面发挥了重要的作用。

CYPs在人肝中的含量及作用

人肝中各CYP含量



各种CYP在药物代谢中的作用



CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4参与了近90%药物的代谢。

Currently, **18 CYP gene families, CYP1, CYP2, CYP3, CYP4, CYP5, CYP7, CYP8, CYP11, CYP17, CYP19, CYP20, CYP21, CYP24, CYP26, CYP27, CYP39, CYP46 and CYP51** have been identified in fish (Unoa *et al.*, 2012) .

Fish P450s have provided insights into the regulation of P450 genes by environmental stresses including water pollution.

Gene family	Gene symbol	Species
CYP1	CYP1A	Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
Xenobiotic		rainbow trout (<i>Oncorhynchus mykiss</i>) mummichog (<i>Fundulus heteroclitus</i>) European seabass (<i>Dicentrarchus labrax</i>) atlantic salmon (<i>Salmo salar</i>) medaka (<i>Oryzias latipes</i>) yellow catfish (<i>Siluriformes</i>) crucian carp (<i>hybridized Prussian carp</i>) mangrove killifish (<i>Rivulus marmoratus</i>)
	CYP1B	scup (<i>Stenotomus chrysops</i>) European plaice (<i>Pleuronectes platessa</i>) marine flatfish (<i>Pleuronectes platessa</i>) carp (<i>Cyprinus carpio</i>) Japanese pufferfish (<i>Takifugu rubripes</i>) mummichog (<i>Fundulus heteroclitus</i>) zebrafish (<i>Danio rerio</i>)
	CYP1C	scup (<i>Stenotomus chrysops</i>) carp (<i>Cyprinus carpio</i>) mummichog (<i>Fundulus heteroclitus</i>) Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
	CYP1D	three-spined stickleback (<i>Gasterosteus aculeatus</i>) medaka (<i>Oryzias latipes</i>) zebrafish (<i>Danio rerio</i>) mummichog (<i>Fundulus heteroclitus</i>)

CYP2	CYP2K	rainbow trout (<i>Oncorhynchus mykiss</i>) zebrafish (<i>Danio rerio</i>) Japanese pufferfish (<i>Takifugu rubripes</i>) rainbow trout (<i>Oncorhynchus mykiss</i>)
Xenobiotic	CYP2M	
	CYP2N	mummichog (<i>Fundulus heteroclitus</i>) largemouth bass (<i>Micropterus salmoides</i>) Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
	CYP2P	mummichog (<i>Fundulus heteroclitus</i>) largemouth bass (<i>Micropterus salmoides</i>) Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
	CYP2R	Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
	CYP2U	Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
	CYP2X	channel catfish (<i>Ictalurus punctatus</i>) Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
	CYP2Z	Japanese pufferfish (<i>Takifugu rubripes</i>) Japanese pufferfish (<i>Takifugu rubripes</i>) zebrafish (<i>Danio rerio</i>)
	CYP2Y,2U1,	
	CYP2AA,2AD, 2AE	zebrafish (<i>Danio rerio</i>)

2007年，第一个甲壳动物水蚤基因组mRNA数据被公布，进行氨基酸序列对比，发现了71个P450基因。

家族名称	可能的 P450 数目	亚家族名称	可能的 P450 数目	所占比例
<i>CYP4</i>	35	<i>CYP4C</i>	30	49.3%
		<i>CYP4V</i>	5	
<i>CYP15</i>	11	<i>CYP15A</i>	11	15.5%
<i>CYP3</i>	10	<i>CYP3A</i>	10	14.1%
<i>CYP2</i>	3	<i>CYP2J</i>	2	4.2%
		<i>CYP2G</i>	1	
<i>CYP5</i>	2	<i>CYP5A</i>	2	2.8%
<i>CYP301</i>	1	<i>CYP301B</i>	1	1.4%
<i>CYP12</i>	1	<i>CYP12H</i>	1	1.4%
<i>CYP302</i>	1	<i>CYP302A</i>	1	1.4%
<i>CYP314</i>	1	<i>CYP314A</i>	1	1.4%
<i>CYP18</i>	1	<i>CYP18A</i>	1	1.4%
<i>CYP306</i>	1	<i>CYP306A</i>	1	1.4%
<i>CYP71</i>	1	<i>CYP71AT</i>	1	1.4%
<i>CYP353</i>	1	<i>CYP353A</i>	1	1.4%
<i>CYP307</i>	1	<i>CYP307A</i>	1	1.4%
<i>CYP315</i>	1	<i>CYP315A</i>	1	1.4%



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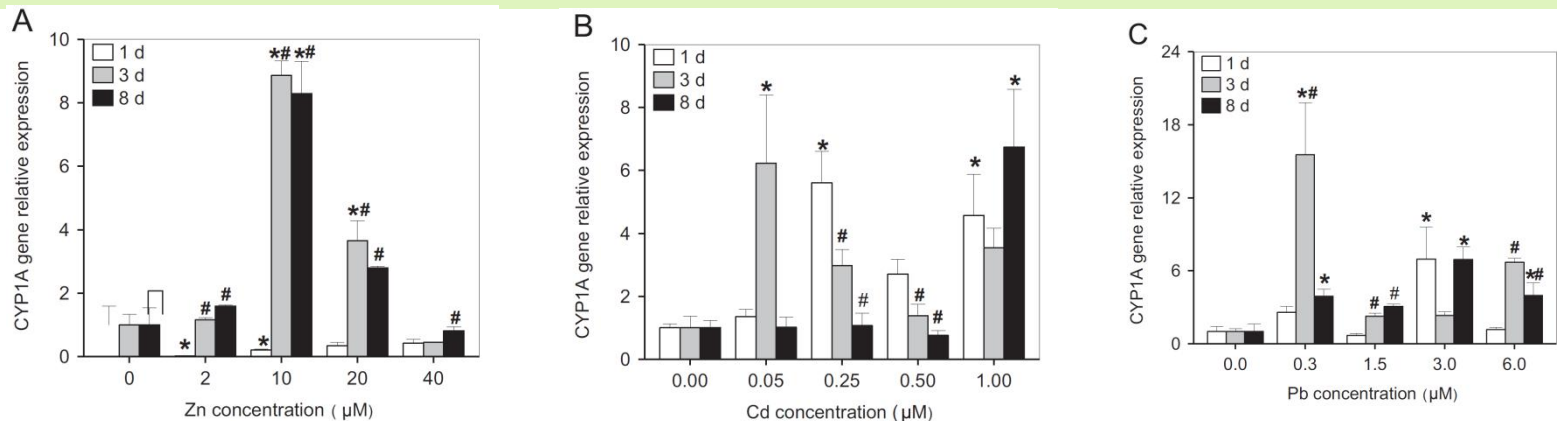
Expression patterns of metallothionein, cytochrome P450 1A and vitellogenin genes in western mosquitofish (*Gambusia affinis*) in response to heavy metals

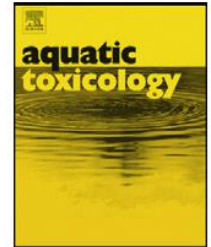


Guo-Yong Huang, Guang-Guo Ying*, Yan-Qiu Liang, Shuang-Shuang Liu, You-Sheng Liu

State Key Laboratory of Organic Geochemistry, Guangzhou Institute of Geochemistry, Chinese Academy of Sciences, Guangzhou 510640, China

The results showed that **Zn, Cd and Pb** could significantly induced **CYP1A mRNA expression** levels in mosquitofish (食蚊鱼).





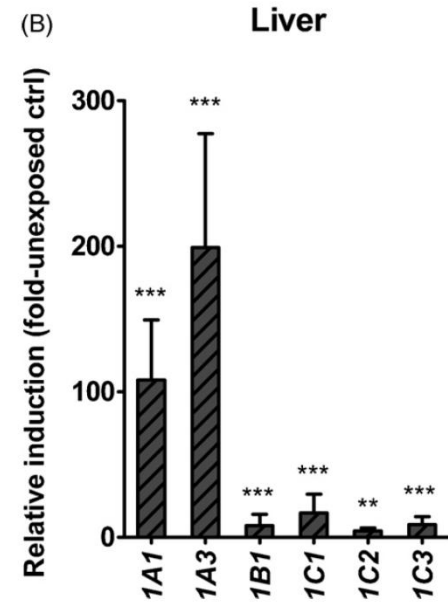
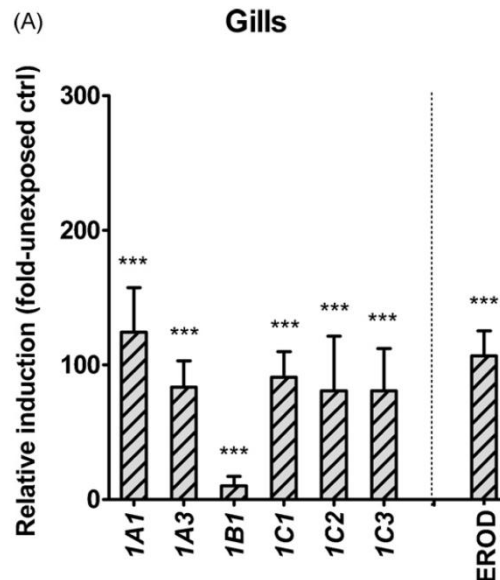
Induction patterns of new CYP1 genes in environmentally exposed rainbow trout

Maria E. Jönsson^{a,*}, Kai Gao^a, Jan A. Olsson^a, Jared V. Goldstone^b, Ingvar Brandt^a

^a Department of Environmental Toxicology, Evolutionary Biology Centre, Uppsala University, Norbyvägen 18A, 752 36 Uppsala, Sweden

^b Biology Department, Redfield 3-42, MS #32, Woods Hole Oceanographic Institution, Woods Hole, MA 02543, USA

Exposure to PCB126



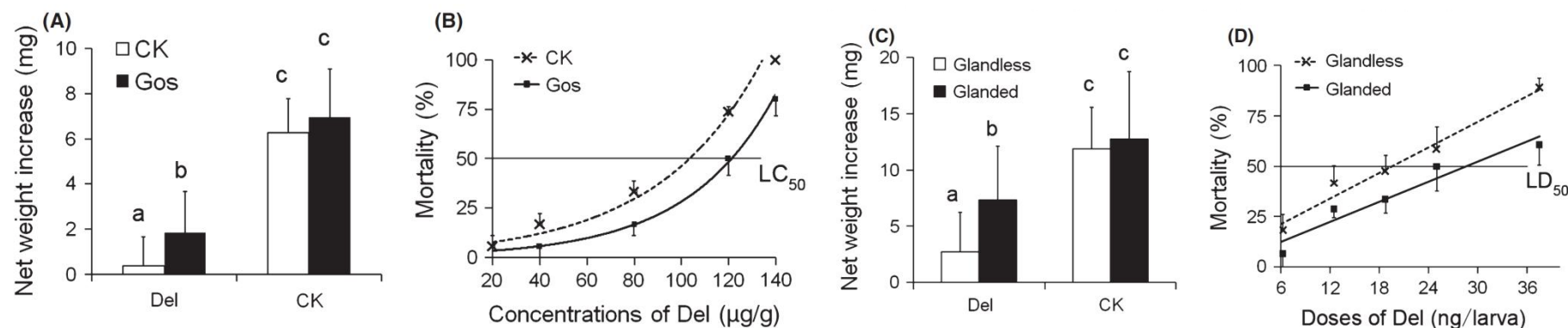
In mammals, CYP2B genes are induced by phenobarbital (PB)(苯巴比妥) and a large number of structurally diverse xenochemicals. In contrast, in fish, expression of CYP2 family mRNAs is not induced by PB-type inducers. Thus, in fish, the CYP2 family catalyzes foreign and endogenous compounds, but the gene regulatory systems may be different from those of mammals (Unoa *et al.*, 2012).

In mammals, expression of the CYP3A subfamily is induced by dexamethasone and rifampicin. Control of CYP3A expression is thought to be mediated by the Ah receptor/ARNT pathway in zebrafish, whereas, the pregnane X receptor (PXR) is suggested to activate CYP3A expression in *Atlantic salmon* (Finn, 2007)

Peroxisome proliferator-activated receptor alpha (PPARalpha), which is the transcriptional factor of the CYP4 family in mammals, has been shown by the use of anti-PPAR antibodies to be distributed primarily in the liver and intestinal tract in zebra fish (Ibabe *et al.*, 2002).

Gossypol-enhanced P450 gene pool contributes to cotton bollworm tolerance to a pyrethroid insecticide (Tao *et al.*, 2012)

The late 2nd instar larvae had previously fed on control (CK) or 1.0 mg/g gossypol-supplemented (Gos) diet for 1 day.



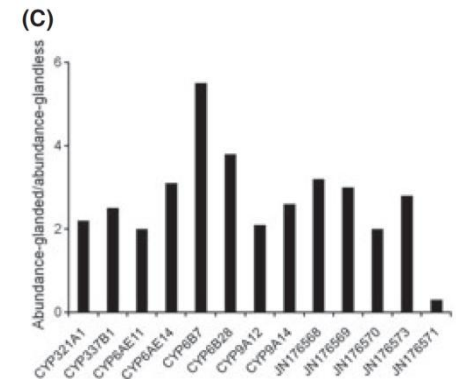
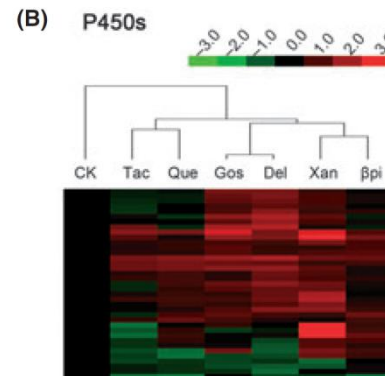
Gossypol-ingested cotton bollworm larvae showed higher midgut P450 enzyme activities and exhibited enhanced tolerance to **deltamethrin** (溴氰菊酯).

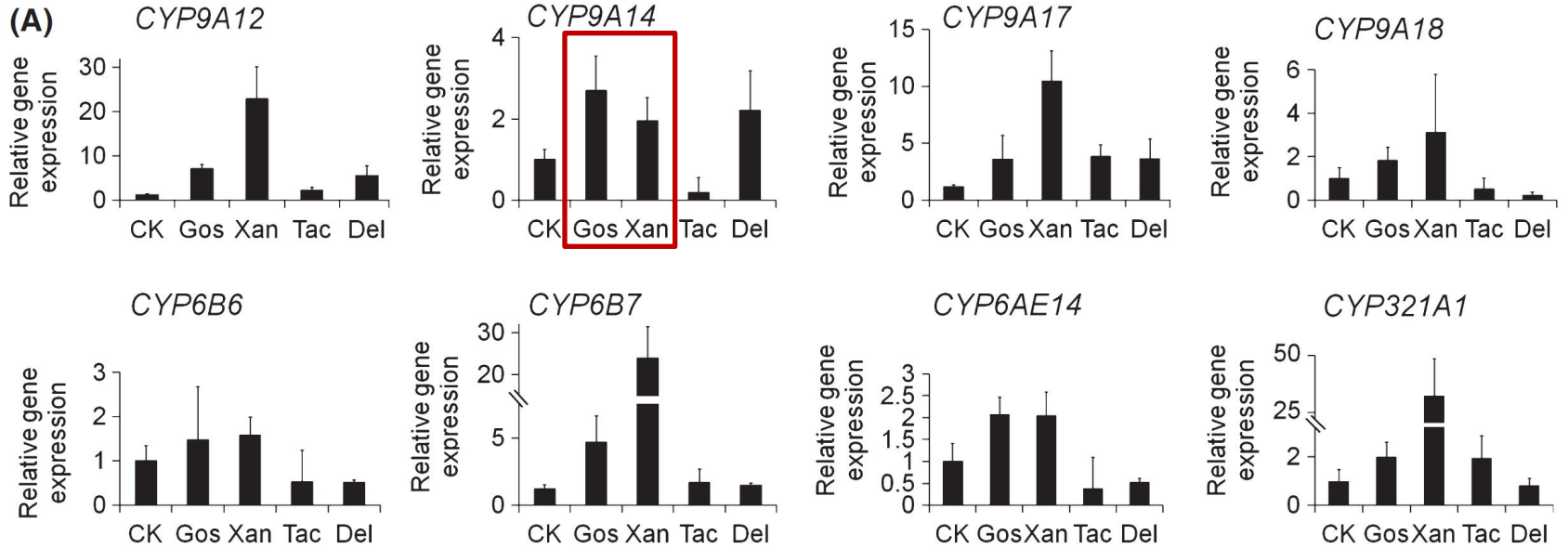
To illustrate the gossypol-induced defence reactions at gene expression level, microarrays were used to analyse the changes in transcript abundance in midgut in response to five phytochemicals (gossypol, xanthotoxin, tannic acid, quercetin and b-pinene) and the insecticide deltamethrin.

Among the 6490 genes analysed, gossypol **upregulated 98** and **downregulated 55**.

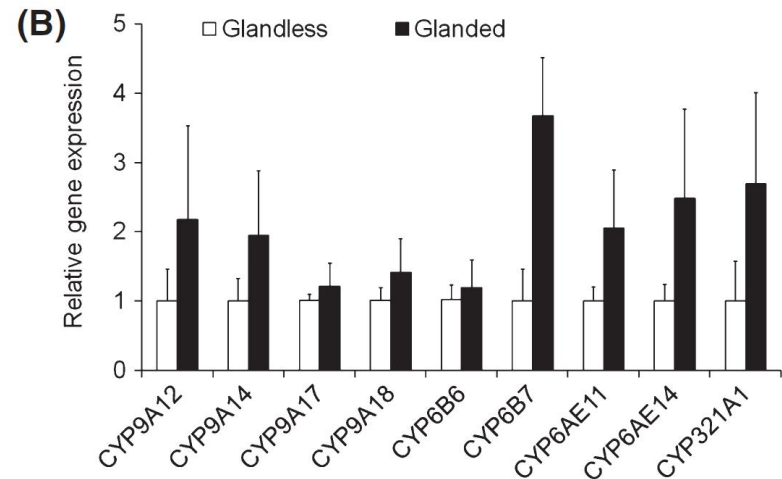
The microarray analysis totally uncovered **37** differentially regulated putative **P450 genes**, which belong to CYP6A, CYP6B, CYP9A, CYP337B and CYP321A subfamilies.

Gossypol upregulated 20 putative P450 Genes.





CYP9A14 was chosen because it was overexpressed in the pyrethroid resistance strains (Yang *et al.* 2006) and its expression was inducible by both gossypol and deltamethrin.

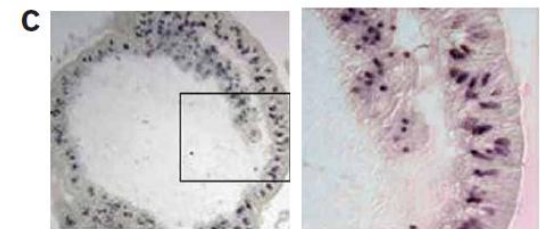
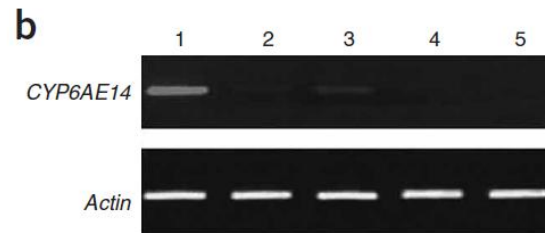
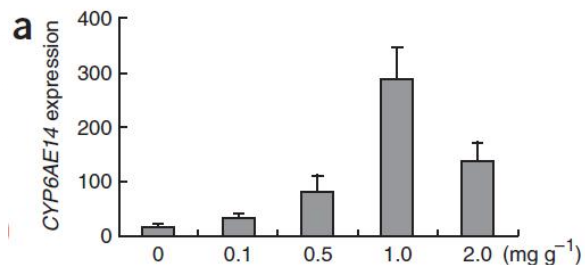


To test this hypothesis, we generated transgenic *Arabidopsis* (拟南芥) plants expressing dsRNA against CYP9A14 (dsCYP9A14).

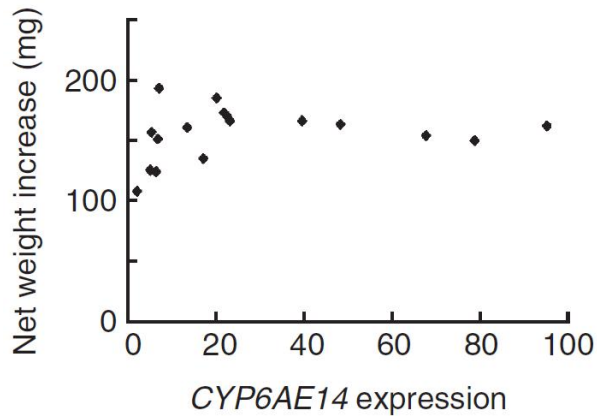
Data presented herein demonstrate the bollworm tolerance of deltamethrin (溴氰菊酯) can be reduced by engineering plant-mediated RNAi against gossypol-inducible P450s.

Silencing a cotton bollworm P450 monooxygenase gene by plant-mediated RNAi impairs larval tolerance of gossypol (Mao *et al.*,2007)

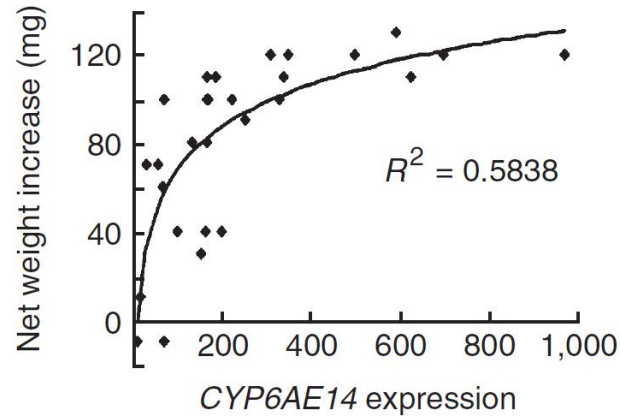
Induction of CYP6AE14 expression by gossypol is dose dependent in the range of 0.1 to 1 mg/g (Fig. a). CYP6AE14 transcript level was **high** in the **midgut**, **low** in **malpighian tubes** and **fatty bodies**, and **undetectable** in the **ovary and brain** (Fig. b). Immunohistochemistry revealed that CYP6AE14 proteins are densely localized on the inner surface of the midgut (Fig. c).



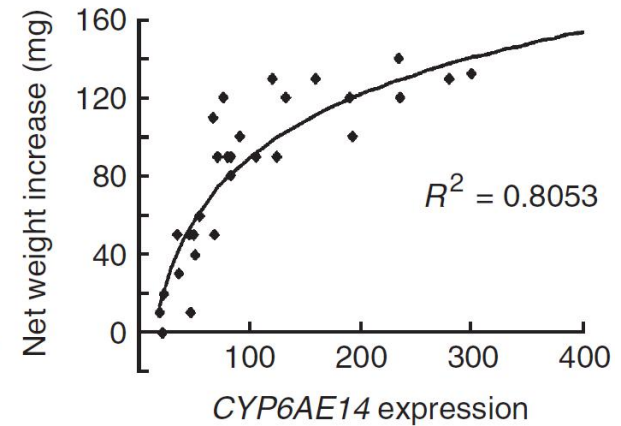
Larval weight increase correlated with CYP6AE14 expression levels when gossypol was included in the diet ($r \leq 0.8$; 2mg/g gossypol). However, this correlation was not observed in the absence of gossypol.



control

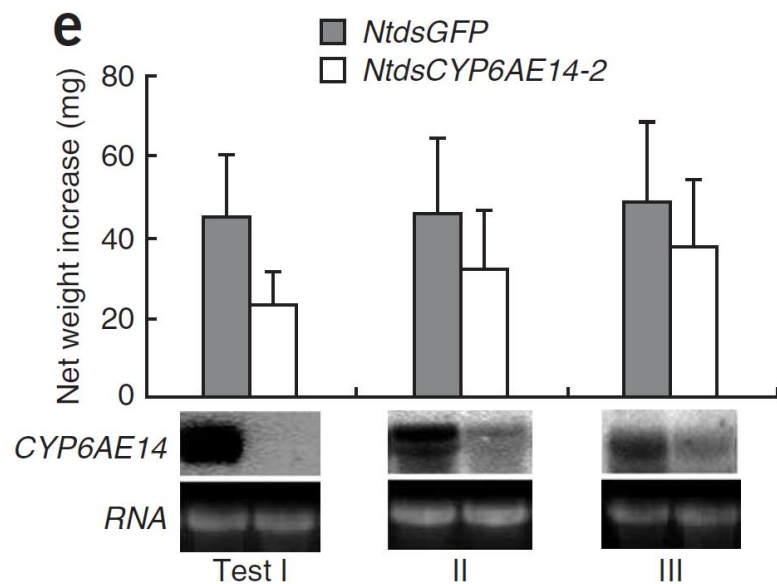
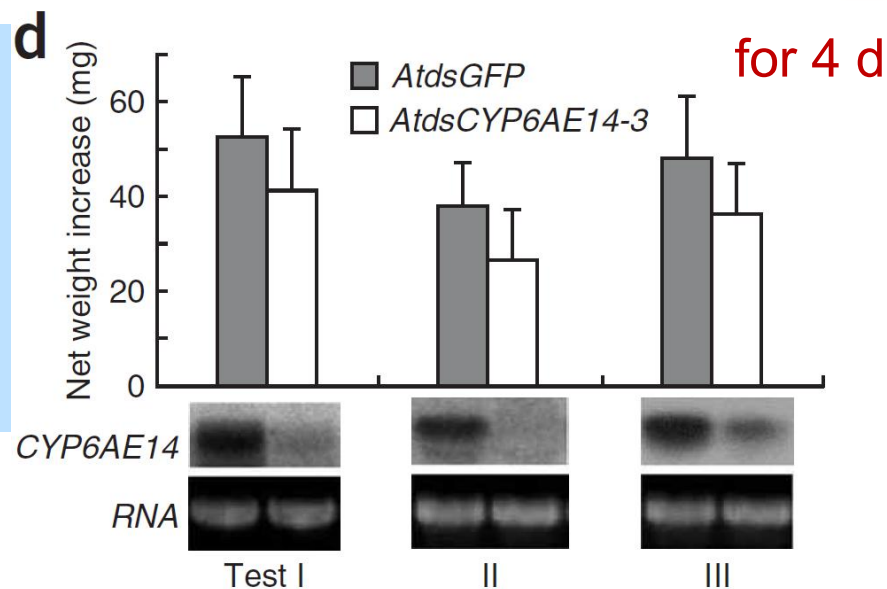
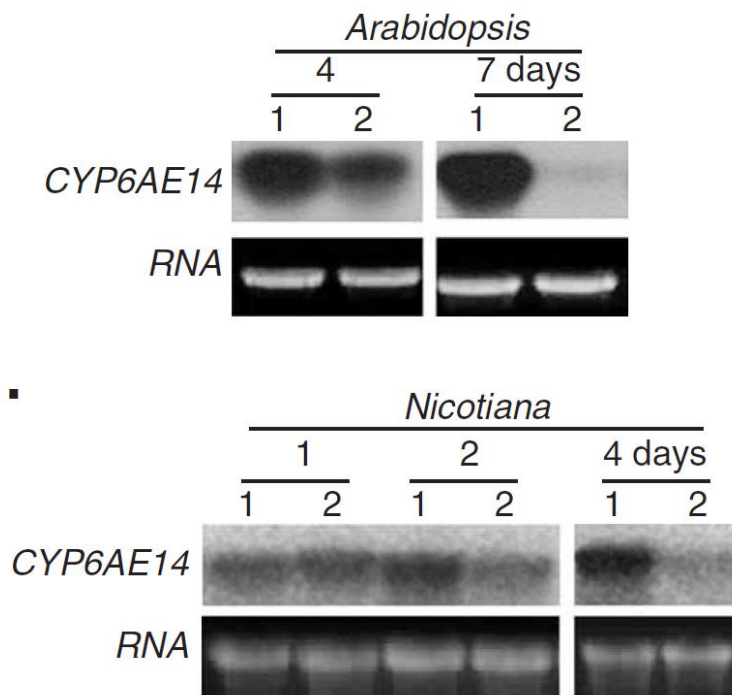


1mg/g gossypol

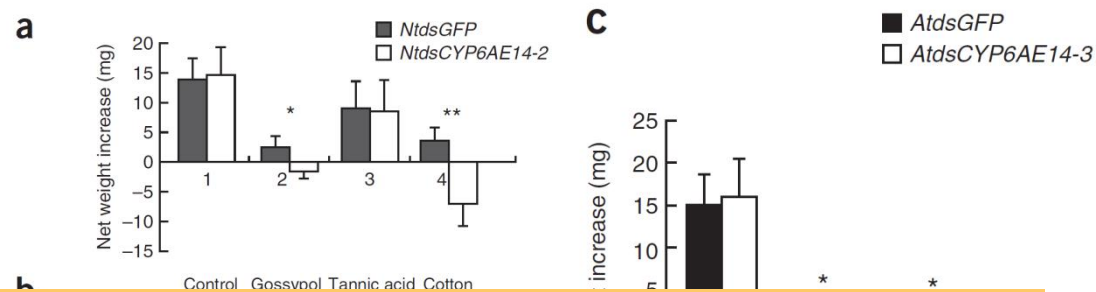


2mg/g gossypol

In comparison with the wild-type plant leaves, larval growth was slightly affected by feeding on dsCYP6AE14 **for 4 d**, but not by dsGFP expression.

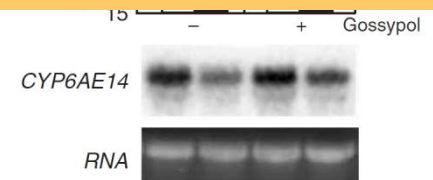


We transferred larvae reared on tobacco (NtdsCYP6AE14-2 and NtdsGFP) leaves for 4 d to artificial diets containing



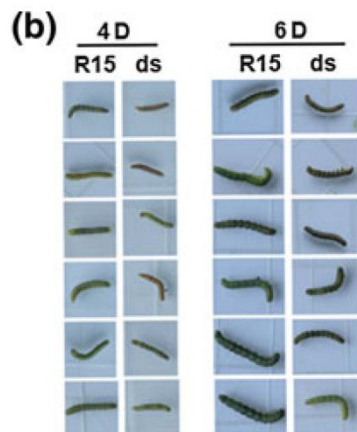
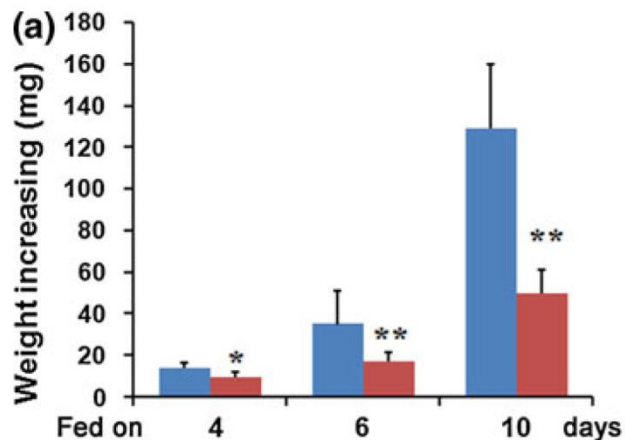
Bollworms fed on transgenic dsCYP6AE14 plants showed suppressed CYP6AE14 expression and reduced growth on gossypol-containing diet.

Their average weight even decreased, whereas growth of NtdsGFP larvae was retarded.



E14-3

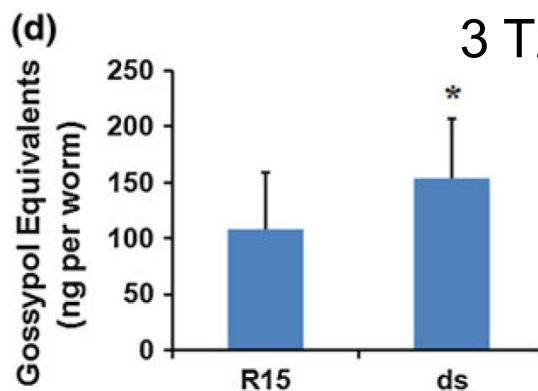
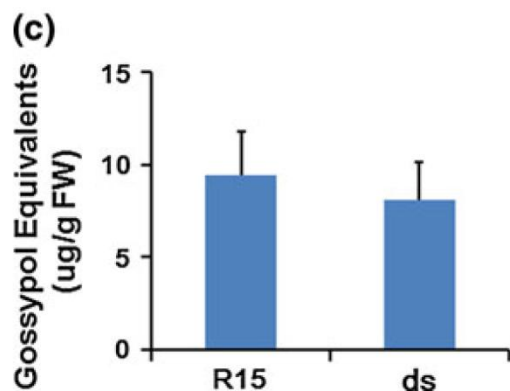
Cotton plants expressing CYP6AE14 double-stranded RNA show enhanced resistance to bollworms (Mao *et al.*, 2011)



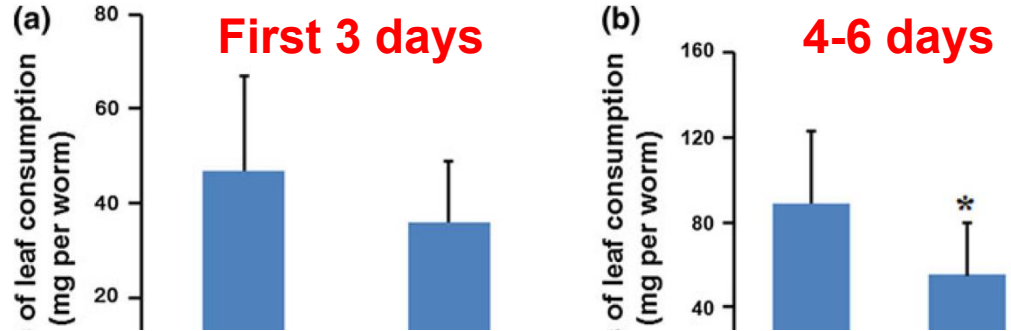
Cotton plants (*Gossypium hirsutum* cv. R15)

dsRNA-expressing cotton (*G.hirsutum*) (T2 plants of the ds6-3 line)

leaves of nontransgenic control **R15 (blue)** or ds6-3 T2 **(ds) plants (red)**

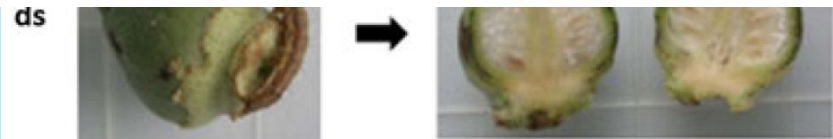


Second-instar larvae were transferred to ds6-3 leaves; during the first 3 days of the assay, ingestion of the ds6-3 leaves was reduced by 21%.



Together, these data indicate that the transgenic dsCYP6AE14 cotton plants were less damaged by cotton bollworms in comparison with the untransformed control.

consumed the contents, whereas the larvae from the ds6-3 leaves chewed only shallow gouges in the boll surface, whereas the boll contents were almost intact.



2. II相反应及其代谢酶研究进展

在酶的催化下将内源性的极性小分子如葡萄糖醛酸、硫酸、氨基酸、谷胱甘肽等结合到药物分子中或I相反应的药物代谢产物中，使药物去活化以及产生水溶性的代谢物，有利于从尿和胆汁中排泄，并限制了肠道的吸收。

催化II相反应的酶有许多，其中主要的有：

葡萄糖醛酸转移酶、谷胱甘肽-S-转移酶、磺基转移酶和乙酰基转移酶等。

表 3-1 二相反应的类型

结合类型	酶	功能基团
葡醛酸结合	UDP-葡醛酸转移酶	-OH、-COOH、-NH ₂ 、-SH
糖苷化反应	UDP-糖基转移酶	-OH、-COOH、-SH
硫酸化反应	磺基转移酶	-NH ₂ 、SO ₂ NH ₂ 、OH
甲基化反应	甲基转移酶	-OH、-NH ₂
乙酰化反应	乙酰基转移酶	-NH ₂ 、-SO ₂ NH ₂ 、-OH
氨基酸结合反应		-COOH
谷胱甘肽结合反应	谷胱甘肽-S-转移酶	环氧化物、有机卤化物
脂肪酸结合反应		-OH
缩合反应		各种功能基团

谷胱甘肽-S-转移酶 (GST) 则是II反应中最主要的代谢酶。GST主要功能为：一方面，催化还原性谷胱甘肽 (GSH) 与毒性化合物的活性产物共轭结合，可减弱毒性，增加水溶性，利于毒物从尿和胆汁排泄，在解毒系统中起重要作用。另一方面，还可催化GSH与亲电中间代谢物的结合，减少这些化合物与细胞内生物大分子如DNA等结合的可能性，清除脂类过氧化物，抑制脂质过氧化作用，间接诱导DNA修复，维持细胞基因组完整性的作用，是抗氧化酶系的组成之一。



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Comparative Biochemistry and Physiology, Part C 150 (2009) 224–230



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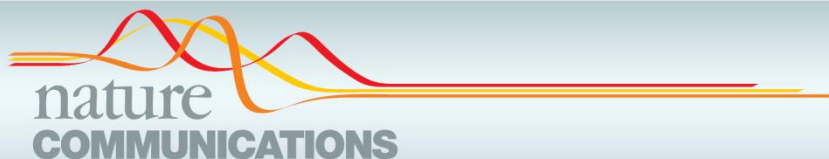
Comparative Biochemistry and Physiology, Part C

Comparative Biochemistry and Physiology, Part C 189 (2016) 31–43



Contents lists available at [ScienceDirect](#)

Comparative Biochemistry and Physiology, Part C



ARTICLE

Received 16 Dec 2014 | Accepted 1 Sep 2016 | Published 5 Oct 2016

DOI: [10.1038/ncomms13084](https://doi.org/10.1038/ncomms13084)

OPEN

Mechanistic evaluation and transcriptional signature of a glutathione S-transferase omega 1 inhibitor

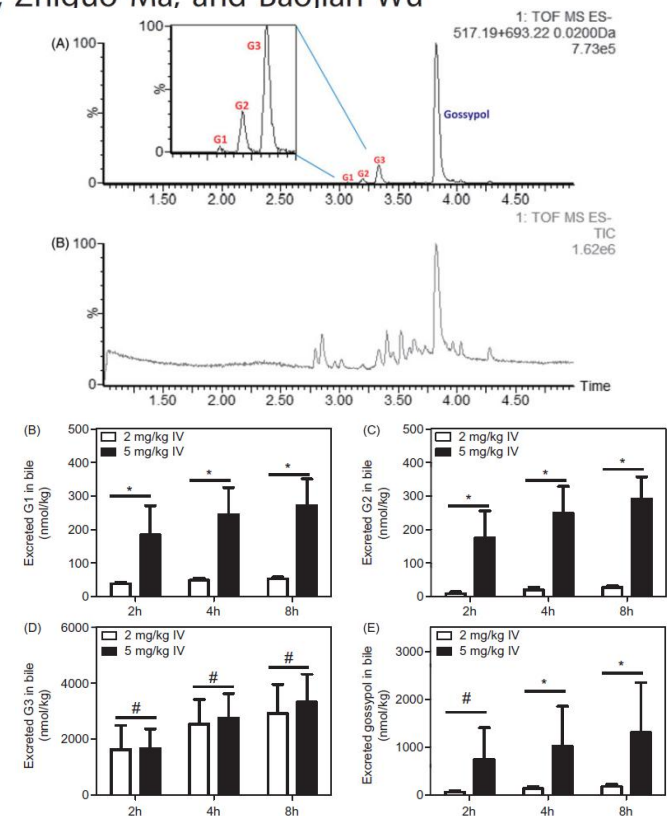
RESEARCH ARTICLE

Identification of glucuronidation and biliary excretion as the main mechanisms for gossypol clearance: *in vivo* and *in vitro* evidence

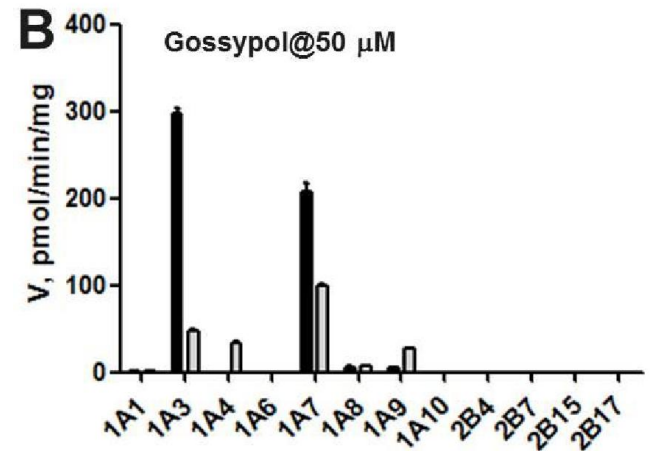
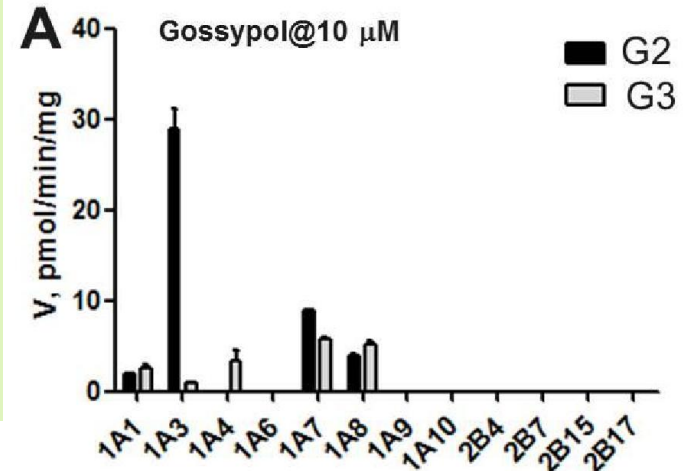
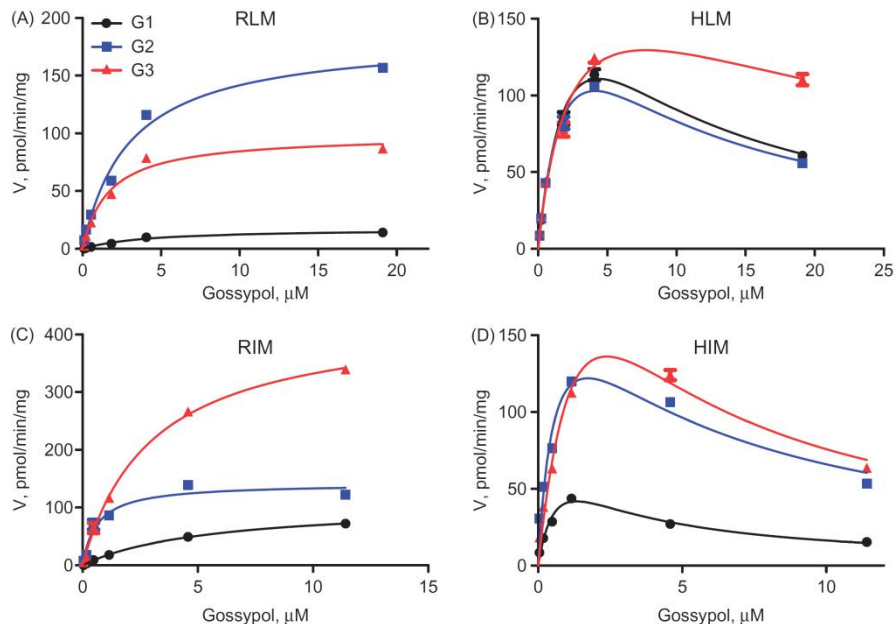
Hongming Liu, Hua Sun, Danyi Lu, Yuchen Zhang, Xingwang Zhang, Zhiquo Ma, and Baojian Wu

Division of Pharmaceutics, College of Pharmacy, Jinan University, Guangzhou, China

In bile duct cannulated rats, considerable amounts of **glucuronides**(葡萄糖醛酸) (G1, G2 and G3; 58.8–83.2% of dose) and parent compound (5.0–20%) were excreted into bile after IV administration.

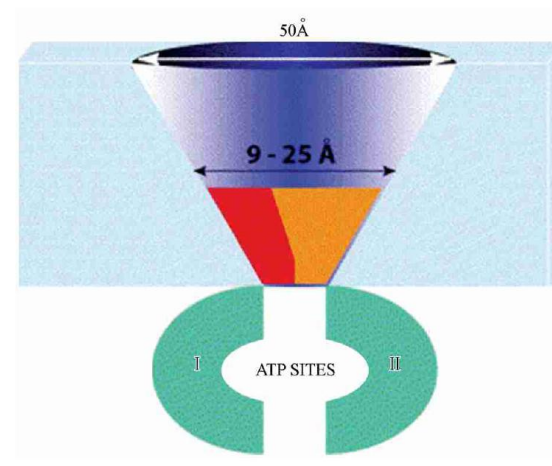
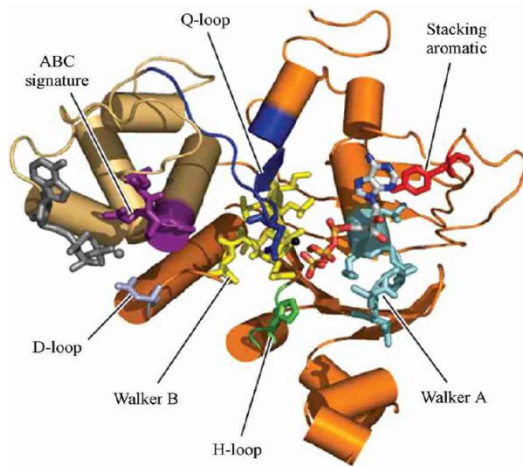


Further, **gossypol** was subjected to rapid **glucuronidation** (葡萄糖酸结合反应) by liver and intestine microsomes. Reaction phenotyping showed that multiple **UGT1A enzymes** (including UGT1A1, 1A3, 1A7 and 1A8) are mainly responsible for gossypol metabolism.



3. III相反应及其代谢酶研究进展

位于细胞膜上的药物转运蛋白ABC是III相反应中主要的药物外排载体，参与各种结构类型的毒物、药物、代谢物和化合物的外排。



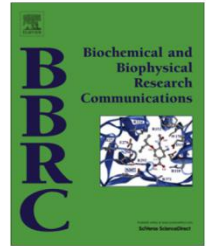
P-gp最早于1976年在中国仓鼠(*Cricetulus*)卵巢中发现。



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Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc



Co-treatment with the anti-malarial drugs mefloquine and primaquine highly sensitizes drug-resistant cancer cells by increasing P-gp inhibition



Ju-Hwa Kim^a, Ae-Ran Choi^a, Yong Kee Kim^b, Sungpil Yoon^{a,*}

^a Research Institute, National Cancer Center, Ilsan-gu, Goyang-si, Gyeonggi-do, Republic of Korea

^b College of Pharmacy, Sookmyung Women's University, Seoul, Republic of Korea

The results demonstrated that the PRI (伯氨喹) and MEF (甲氟喹) sensitisation mechanism mainly depends on the inhibition of p-glycoprotein (P-gp).



OPEN

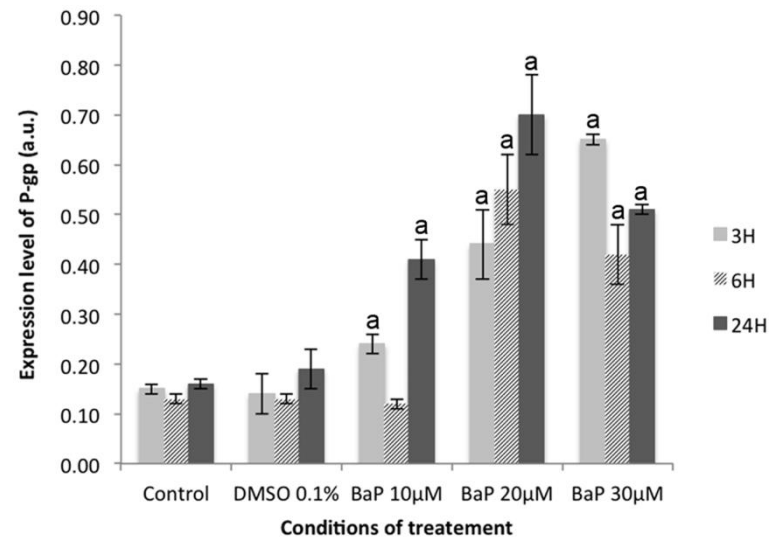
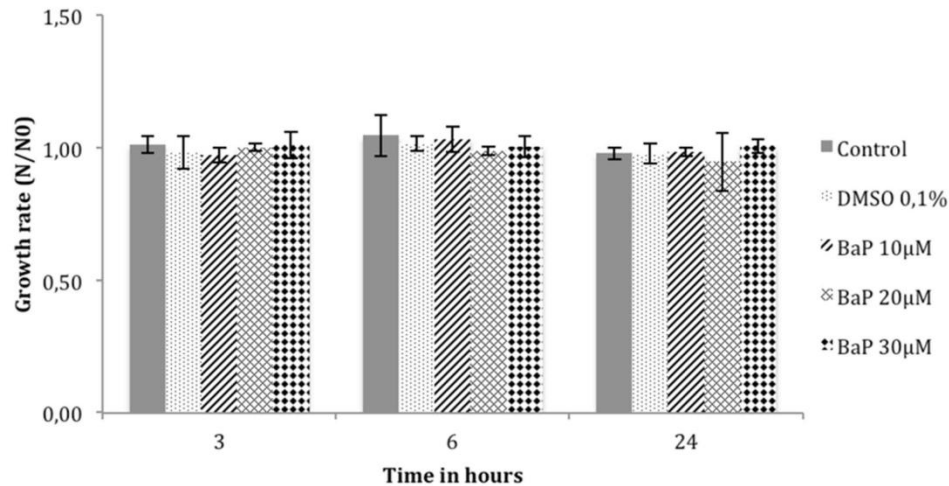
P-gp expression in brown trout erythrocytes: evidence of a detoxification mechanism in fish erythrocytes

SUBJECT AREAS:
PROTEIN TRANSPORT
ENVIRONMENTAL
BIOTECHNOLOGY
TRANSPORTERS
PROTEIN TRANSPORT

Emeline Valton^{1,2,3}, Christian Amblard³, Ivan Wawrzyniak³, Frederique Penault-Llorca^{1,2}
& Mahchid Bamdad^{1,2,3*}

The results showed that in the presence of **BaP**(苯并芘) at 10, 20 and 30 mM, the number of cells **remained stable** over time without signs of BaP toxicity.

In the presence of both 20 and 30 mM BaP, **P-gp expression was clearly induced** during the experiment.

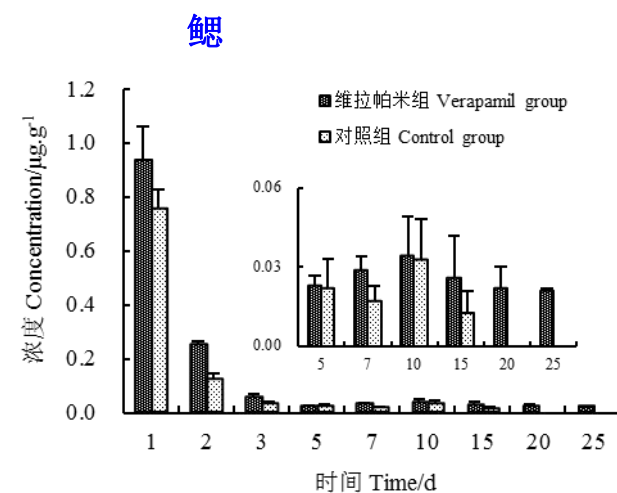
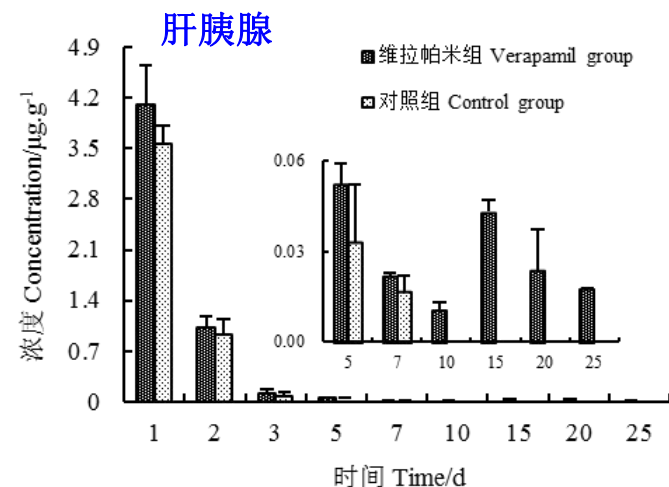


维拉帕米可降低恩诺沙星的代谢和消除速率，同时可增加药物在体内的残留量。推测脊尾白虾P-gp可介导恩诺沙星及代谢物环丙沙星的外排。

Tab.1 Statistical moment parameters of enrofloxacin and its metabolite ciprofloxacin in *Exopalaemon carinicauda*

参数 parameters	单位 units	组织 tissues	恩诺沙星 enrofloxacin		环丙沙星 ciprofloxacin	
			对照组 control group	维拉帕米组 verapamil group	对照组 control group	维拉帕米组 verapamil group
峰浓度 peak concentration (C_{max})	$\mu\text{g/g}$	肝胰腺	3.572 ± 0.245	4.101 ± 0.541*	0.292 ± 0.036	0.214 ± 0.034
		肌肉	0.880 ± 0.088	1.545 ± 0.089*	0.018 ± 0.003	0.012 ± 0.002
		鳃	0.754 ± 0.074	0.940 ± 0.12*	0.146 ± 0.010	0.029 ± 0.009*
达峰时间 time to peak concentration (t_{max})	d	肝胰腺	1	1	1	1
		肌肉	1	1	1	1
		鳃	1	1	1	1
消除速率常数 elimination rate constant	/d	肝胰腺	1.157 ± 0.036	0.109 ± 0.014*	0.158	0.025*
		肌肉	0.509 ± 0.015	0.129 ± 0.001*	-	-
		鳃	0.066 ± 0.011	0.018 ± 0.004*	0.166	-
消除半衰期 elimination half-time ($t_{1/2\beta}$)	d	肝胰腺	0.599 ± 0.121	6.331 ± 0.365*	4.376	27.81*
		肌肉	1.361 ± 0.265	5.364 ± 0.845*	-	-
		鳃	10.495 ± 1.32	38.346 ± 3.154*	4.163	-
药时曲线下面积 area under concentration- time curve (AUC)	$\text{mg}/(\text{L} \cdot \text{d})$	肝胰腺	4.709 ± 1.001	5.986 ± 1.242*	3.142	1.773*
		肌肉	3.555 ± 0.891	5.466 ± 0.988*	-	-
		鳃	1.173 ± 0.325	1.817 ± 0.547*	0.304	-
清除率 clearance rate (CL)	$\text{L}/(\text{d} \cdot \text{kg})$	肝胰腺	4.245 ± 0.987	1.507 ± 0.365*	3.266	3.05*
		肌肉	2.812 ± 0.587	1.823 ± 0.245*	-	-
		鳃	14.645 ± 2.141	6.688 ± 1.254*	28.262	-

注：- 参数值无法拟合。 Note: Parameter values can not be fitted.

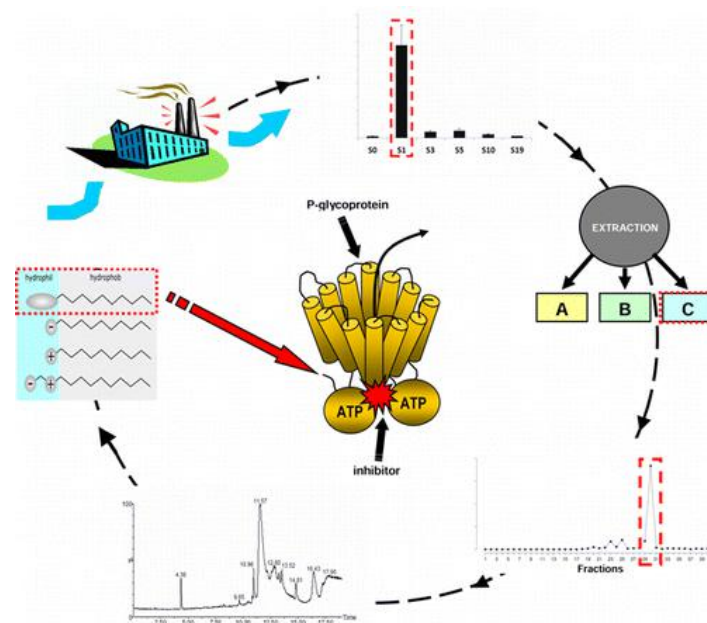


Identification of P-Glycoprotein Inhibitors in Contaminated Freshwater Sediments

Roko Zaja, Senka Terzić, Ivan Senta, Jovica Lončar, Marta Popović, Marijan Ahel, and Tvrtko Smital*

Division for Marine and Environmental Research, Rudjer Boskovic Institute, Zagreb, Croatia

Testing of several commercial mixtures confirmed their potential to **inhibit** the fish **P-glycoprotein** and modulate toxicity of other xenobiotics present in complex environmental samples.



思考：

棉酚在鱼体内如何代谢？

谢 谢

