










**Supplementary information to:**

**Original article:**

**MIXTURE EFFECTS OF CO-FORMULANTS AND TWO PLANT  
PROTECTION PRODUCTS IN A LIVER CELL LINE**

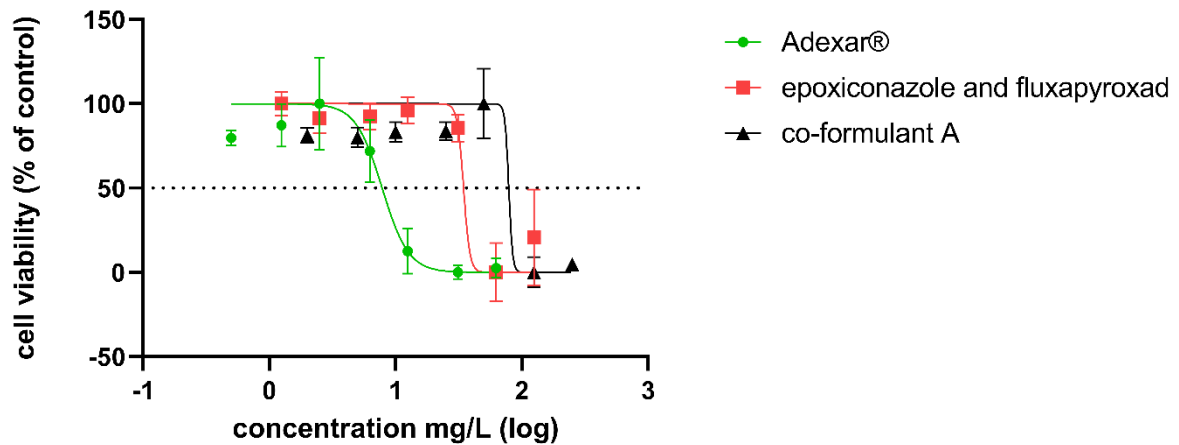
Katreece Feiertag , Mawien Karaca , Benjamin Fischer , Tanja Heise ,  
Denise Bloch , Tobias Opialla , Tewes Tralau , Carsten Kneuer ,  
Philip Marx-Stoelting\* 

German Federal Institute for Risk Assessment, Department Pesticides Safety, Berlin,  
Germany

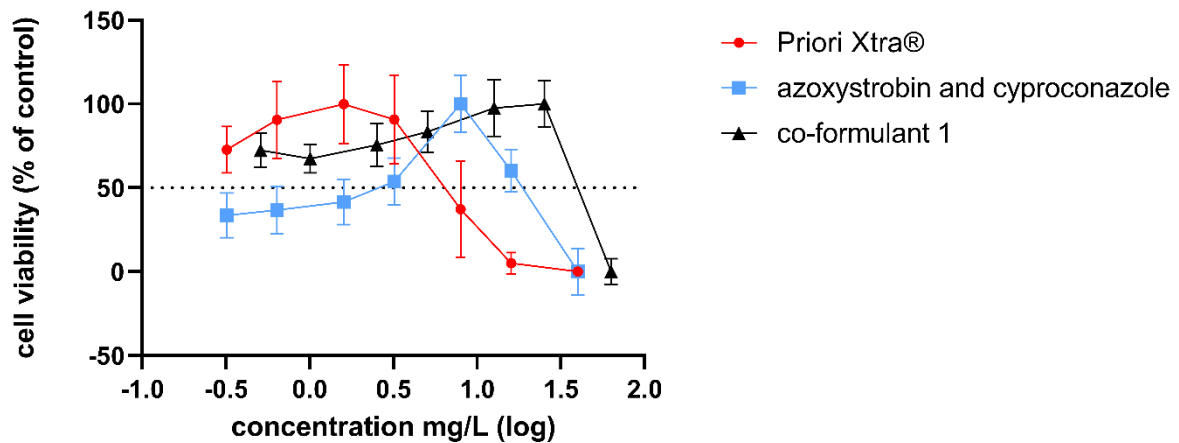
\* **Corresponding author:** Philip Marx-Stoelting, German Federal Institute for Risk  
Assessment, Department Pesticides Safety, Max-Dohrn-Str. 8-10, 10589 Berlin, Germany.  
Tel.: +49 30 1841226600, E-mail: [Philip.Marx-Stoelting@bfr.bund.de](mailto:Philip.Marx-Stoelting@bfr.bund.de)

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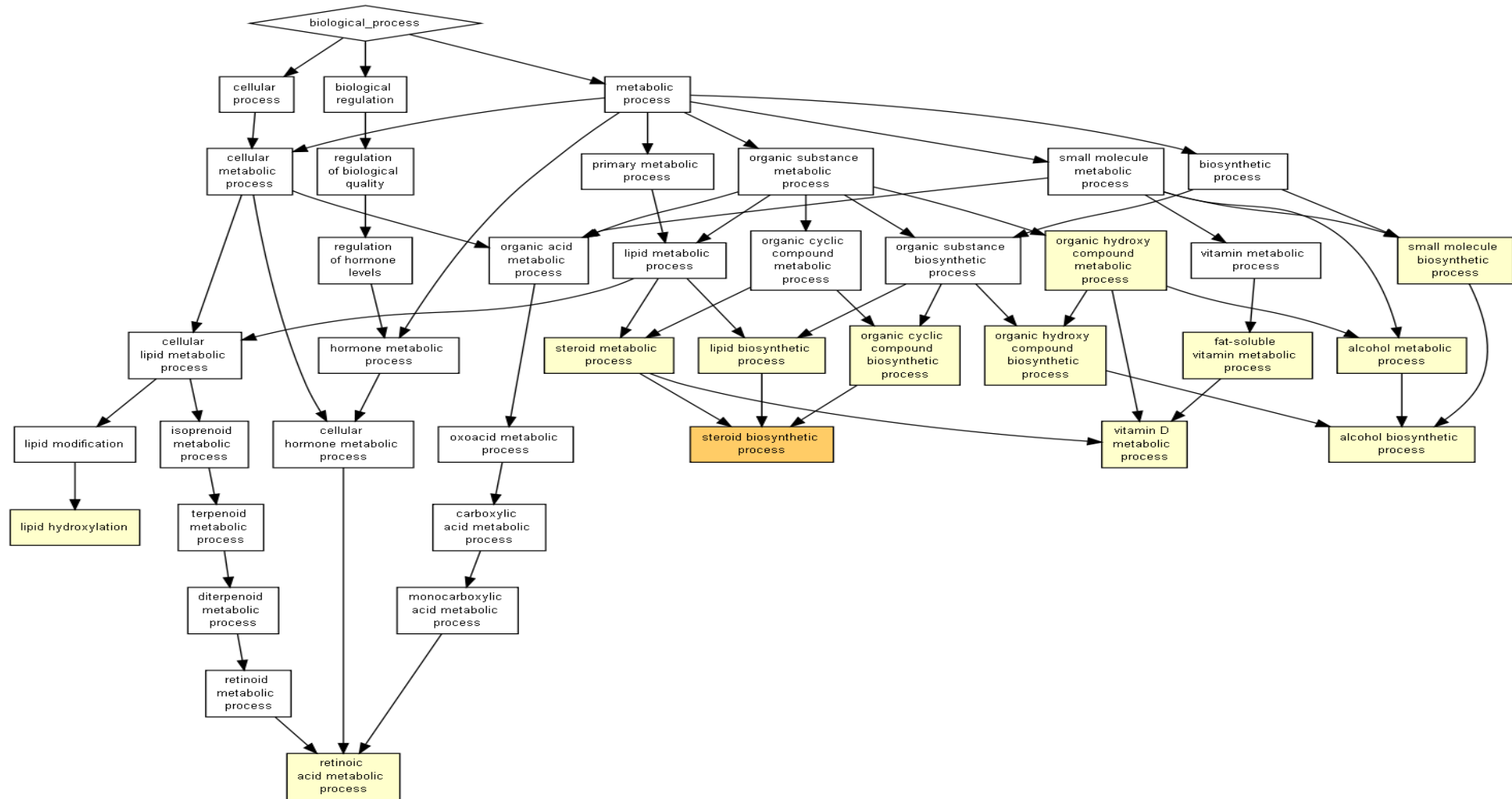
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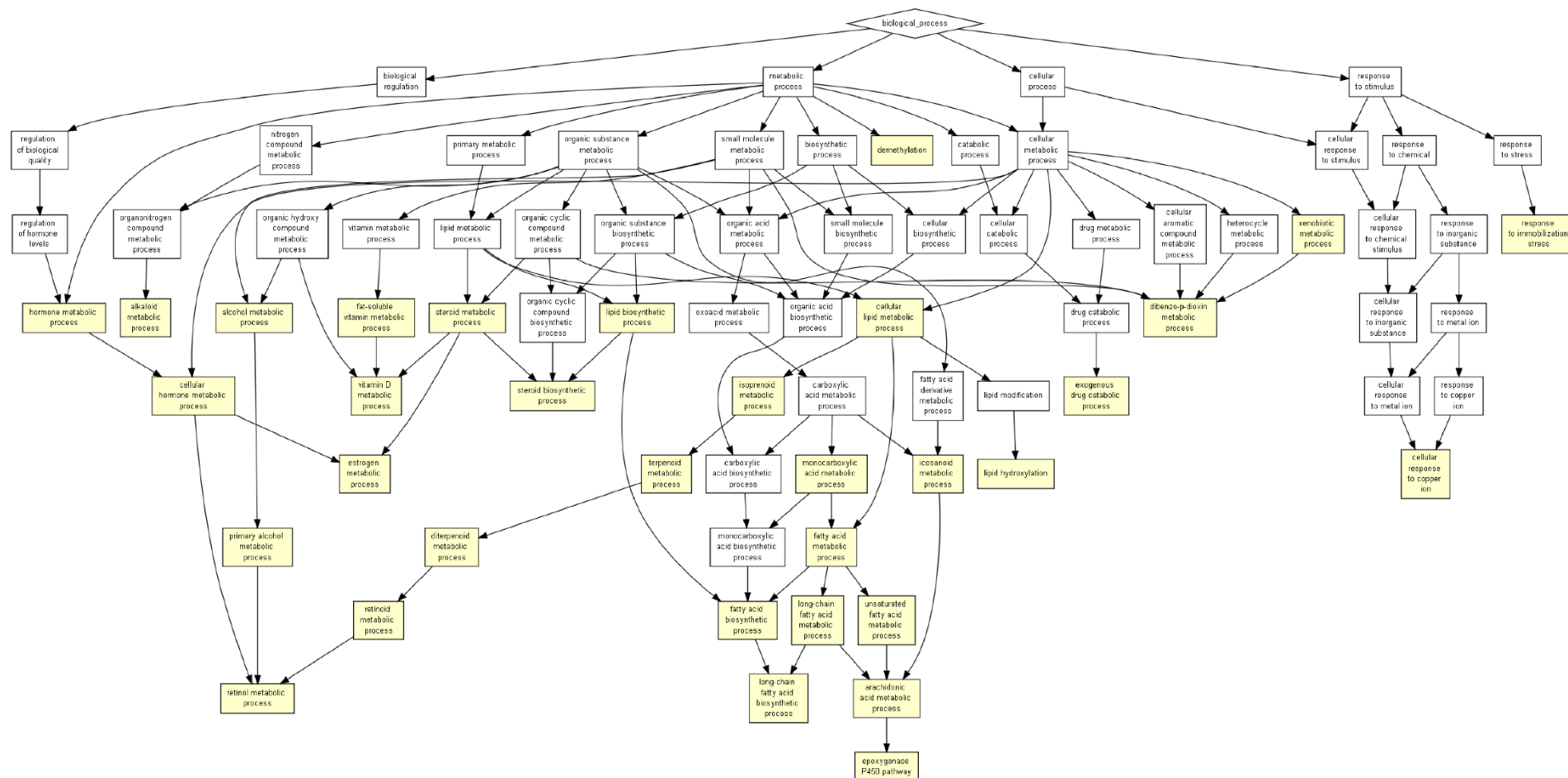
**Supplementary Figure 1:** Cytotoxic effects of Adexar® (green); its active substances' mix (epoxiconazole and fluxapyroxad (red)); and a co-formulant of Adexar® (black) on HepaRG cells after 24 h treatment obtained from WST-1 assay. Concentration data were transformed using  $X=\log(X)$  and then normalized to the solvent control. Error bars indicate standard deviation, n=2 biological replicates each performed with 6 technical replicates. (Concentration of products expressed as the active substances' concentration within the product). Adexar® (a) contains the active substances fluxapyroxad and epoxiconazole in equimolar proportions (each 62.5 g/L).



**Supplementary Figure 2:** Cytotoxic effects of Priori Xtra® (red); its active substances' mix (cyproconazole and azoxystrobin, (blue) and a co-formulant (black) of Priori Xtra® on HepaRG cells after 24 h treatment obtained from NRU assay. Concentration data were transformed using  $X=\log(X)$  and then normalized to the solvent control. Error bars indicate standard deviation, n=2 biological replicates each performed with 6 technical replicates. (Concentration of Priori Xtra® expressed as the active substances' concentration within the product). Priori Xtra® (b) contains ready-to-use 80 g/L cyproconazole and 200 g/L azoxystrobin. Only the concentration of cyproconazole is shown in case of both the mixture and the product.



**Supplementary Figure 3:** GO Term result from gene expression data obtained from cells treated with Adexar® at 1.25mg/L



**Supplementary Figure 4:** GO Term result from gene expression data obtained from cells treated with Epoxiconazole and fluxapyroxad in combination at 1.25mg/L each.

**Supplementary Table 1:** LC Pump Gradient conditions for the active substances azoxystrobin, cyproconazole, epoxiconazole and fluxapyroxad

Total time (min)	% A (0.2% (v/v) formic acid in water)	B % (Methanol)
0.00	40	60
14.00	30	70
14.05	40	60
20.00	40	60

**Supplementary Table 2:** Significantly affected gene transcripts after 24 h treatment with Adexar® (1.25 mg/L (expressed as the active substances' concentration within the product) and epoxiconazole and fluxapyroxad (1.25 mg/L each) in combination. Up and downregulation was considered relevant at <0.5 and >2-fold change in gene expression with significantly upregulated gene transcripts indicated in red.

Adexar®	epoxiconazole and fluxapyroxad
CYP3A4	CYP3A4
CYP1A1	CYP1A1
MSMO1	MSMO1
ACAT2	CYP2B6
	CYP1A2

**Supplementary Table 3:** Significantly affected gene transcripts after 24 h treatment with co-formulant A of Adexar® (50 mg/L) in comparison to the solvent control. Up and downregulation was considered relevant at <0.5 and >2-fold change in gene expression with significantly up and downregulated gene transcripts indicated in red and blue respectively.

Co-formulant A
ACACA
CYP2C19
ACOT12
SERPINA3
GPX2
CTSE
UGT2B4
FABP1