

In silico toxicity prediction using Derek Nexus® for skin sensitization, phototoxicity, hepatotoxicity and in vitro hERG inhibition

Varun Ahuja*¹, Mohan Krishnappa¹, Helena Kandarova²

*Varun.Ahuja@syngeneintl.com

¹Syngene International Ltd, Biocon Park, Bangalore, India. ²Institute of Experimental Pharmacology & Toxicology, Slovak Academy of Sciences, Bratislava, Slovakia

Introduction

- Quick screening of compounds in drug discovery during hit-to-lead identification phase is needed. Also, regulatory agencies promulgate use of non-animal methods for toxicity testing of chemicals.
- We performed *in silico* toxicity evaluation using Derek® Nexus 6.1.1/Derek Knowledge Base 2020 1.0 (Lhasa Limited, UK), aiming for a quicker and cost-effective screening for skin sensitisation, phototoxicity, hepatotoxicity and *in vitro* hERG channel inhibition.

Methods

- Sensitisation screening:** We selected 45 substances including sensitiser and non-sensitiser drugs and chemicals for *in silico* testing for sensitisation potential screening. LLNA data was primarily used for comparison purposes.
- Phototoxicity screening:** 62 substances belonging to various classes i.e. phototoxic/non-phototoxic chemicals and drugs were selected. Published human data for sensitisation was primarily used for comparing with *in silico* results. In case of unavailability of human or animal data for a limited number of substances, *in vitro* data was used for comparison¹.
- hERG channel inhibition screening:** 91 drugs were selected from CredibleMeds list² of drugs as well as from published literature and included drugs positive for hERG block as well as drugs with no effect on hERG.
- Hepatotoxicity screening:** 78 drugs from FDA's Drug Induced Liver Injury Rank (DILIrank)³ dataset of from various categories varying from most/less/no concern for DILI were selected. The selected compounds were further cross-verified from NCI-LiverTox⁴ database for positive/negative hepatotoxicity potential.
- Analysis of Derek outcome:** Prediction of toxicity of various degrees such as probable/plausible/equivocal were considered as positive prediction. A negative result was given in case of no fired alerts. Various DEREK-specific predictions are defined as follows:
 - Plausible: The weight of evidence supports the proposition.
 - Probable: There is at least one strong argument that the proposition is true and there are no arguments against it.
 - Equivocal: There is an equal weight of evidence for and against the proposition.

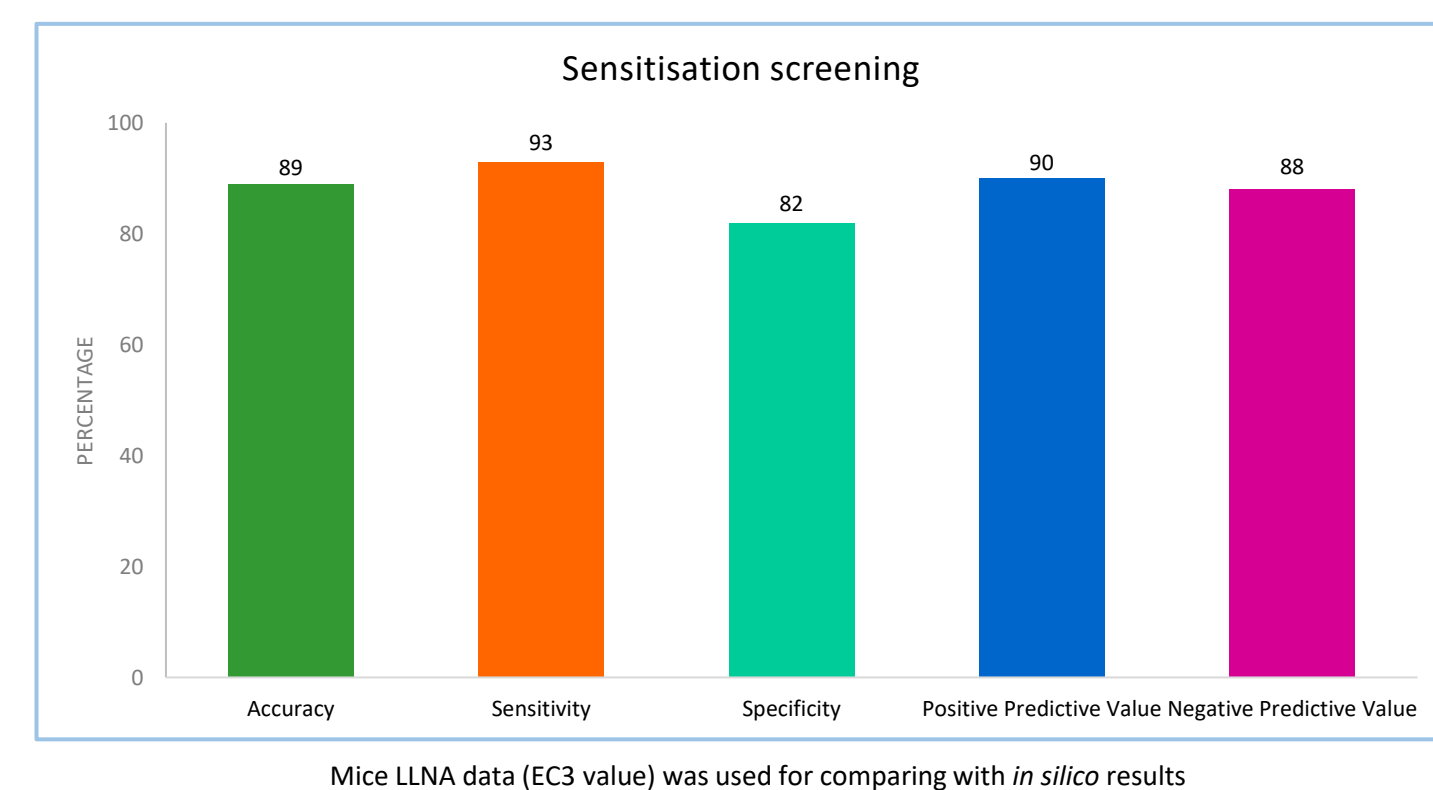
Results

Sensitization screening

Both LLNA and Derek led to classification of tested substances into similar classes of extreme (EC3<0.1), strong (EC3≥0.1 to <1), moderate (EC3≥1 to <10), and weak (EC3≥10 to <100) sensitizers as well as similar GHS classification⁵.

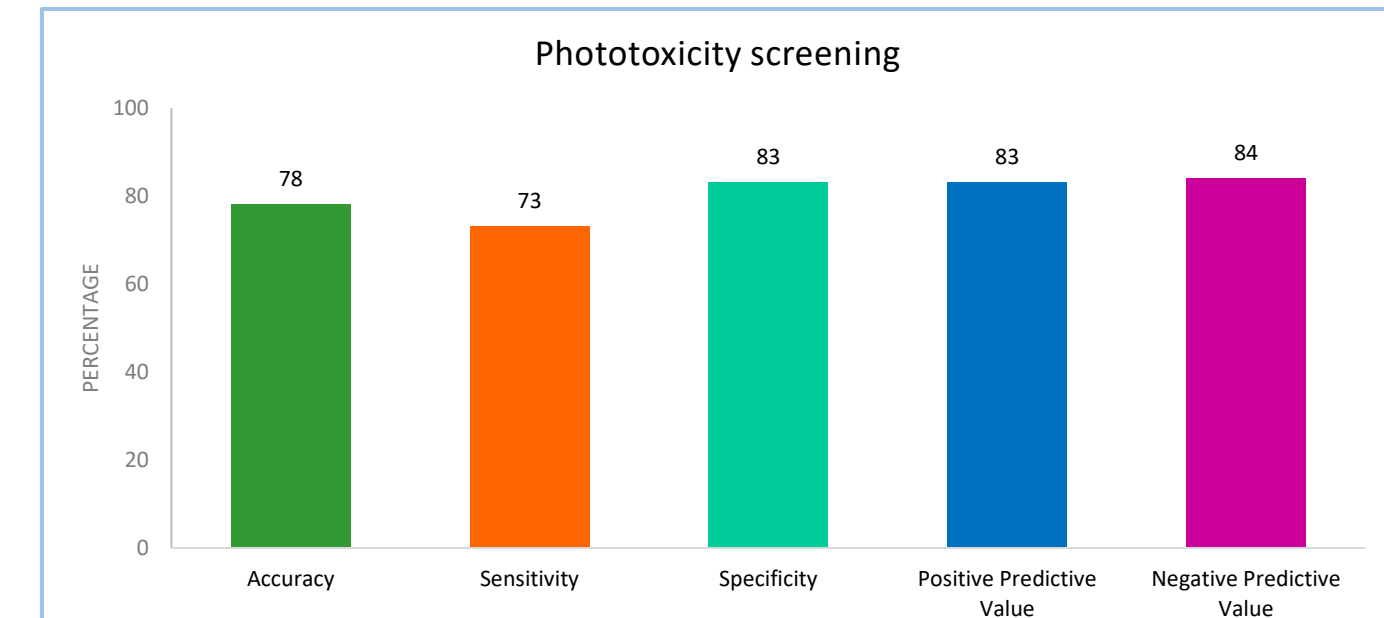
S. No.	Substance	LLNA-EC3 value	LLNA-GHS category	DEREK Prediction	DEREK-EC3 value	DEREK-GHS category
Sensitizers						
1	Beryllium sulfate	0.001	1A	Plausible	8.6	1B
2	Kathon CG 5243	0.009	1A	Probable	0.0095	1A
3	Benzoquinone	0.0099	1A	Probable	0.0099	1A
4	Diphencyclopentone	0.05	1A	Probable	0.003	1A
5	Oxazolone	0.01	1A	Plausible	0.0014	1A
6	4-Phenylenediamine	0.11	1A	Probable	0.09	1A
7	Chlorpromazine HCl	0.14	1A	Non-sensitizer	NA	NA
8	Chloramine T	0.4	1A	Plausible	0.6	1A
9	Formaldehyde	0.61	1A	Plausible	0.4	1A
10	2-Mercaptobenzothiazole	1.7	1A	Non-sensitizer	NA	NA
11	Benzylsallylate	2.9	1B	Equivocal	2.9	1B
12	1-Thioglycerol	3.6	1B	Probable	3.6	1B
13	Dihydroxybenzyl	6.8	1B	Plausible	6.8	1B
14	Phenylacetaldehyde	3	1B	Probable	5.9	1B
15	Cinnamic aldehyde	3.1	1B	Plausible	1.2	1A
16	p-methylhydrocinnamic aldehyde	13.7	1B	Plausible	14	1B
17	Hexylcinnamic aldehyde	14.7	1B	Plausible	9.5	1B
18	Benzylcinamate	18.4	1B	Plausible	18	1B
19	p-tert-Butyl-a-methyl hydrocinnamal	18.7	1B	Plausible	5.5	1B
20	Cyclamen aldehyde	22.3	1B	Probable	22	1B
21	Imidazolidinurea	24	1B	Plausible	Not Available	NA
22	Penicillin G	30	1B	Plausible	20	1B
23	Hydroxycitronellal	33	1B	Plausible	22	1B
24	D-Limonene	69	1B	Probable	30	1B
25	Aniline	89	1B	Probable	33	1B
26	Methylmethacrylate	90	1B	Plausible	75	1B
27	Nickel chloride	NA	1B	Plausible	0.28	1A
28	Beryllium sulfate	0.001	1A	Plausible	8.6	1B

S. No.	Substance	LLNA-EC3 value	GHS Potency category	DEREK Prediction	DEREK-EC3 value	DEREK-GHS category
Non-sensitizers						
29	Glycerol	NA	Not classified	Non-sensitizer	NA	NC
30	2,4-Dichloronitrobenzene	NA	Not classified	Plausible	20	1B
31	Benzyl alcohol	NA	Not classified	Non-sensitizer	NA	NC
32	Methylsallylate	NA	Not classified	Non-sensitizer	NA	NC
33	Isopropanol	NA	Not classified	Non-sensitizer	NA	NC
34	Dimethylisophthalate	NA	Not classified	Non-sensitizer	NA	NC
35	4-Aminobenzoic acid	NA	Not classified	Equivocal	15	1B
36	Lactic acid	NA	Not classified	Non-sensitizer	NA	NC
37	Citric acid	NA	Not classified	Non-sensitizer	NA	NC
38	Sulfanilic acid	NA	Not classified	Equivocal	39	1B
39	Vanillin	NA	Not classified	Non-sensitizer	NA	NC
40	Polyethylene glycol	NA	Not classified	Non-sensitizer	NA	NC
41	Streptomycin sulfate	NA	Not classified	Non-sensitizer	NA	NC
42	Saccharin	NA	Not classified	Non-sensitizer	NA	NC
43	Glycerol	NA	Not classified	Non-sensitizer	NA	NC
44	Benzoic acid	NA	Not classified	Non-sensitizer	NA	NC
45	1-Bromobutane	NA	Not classified	Non-sensitizer	NA	NC



Phototoxicity screening

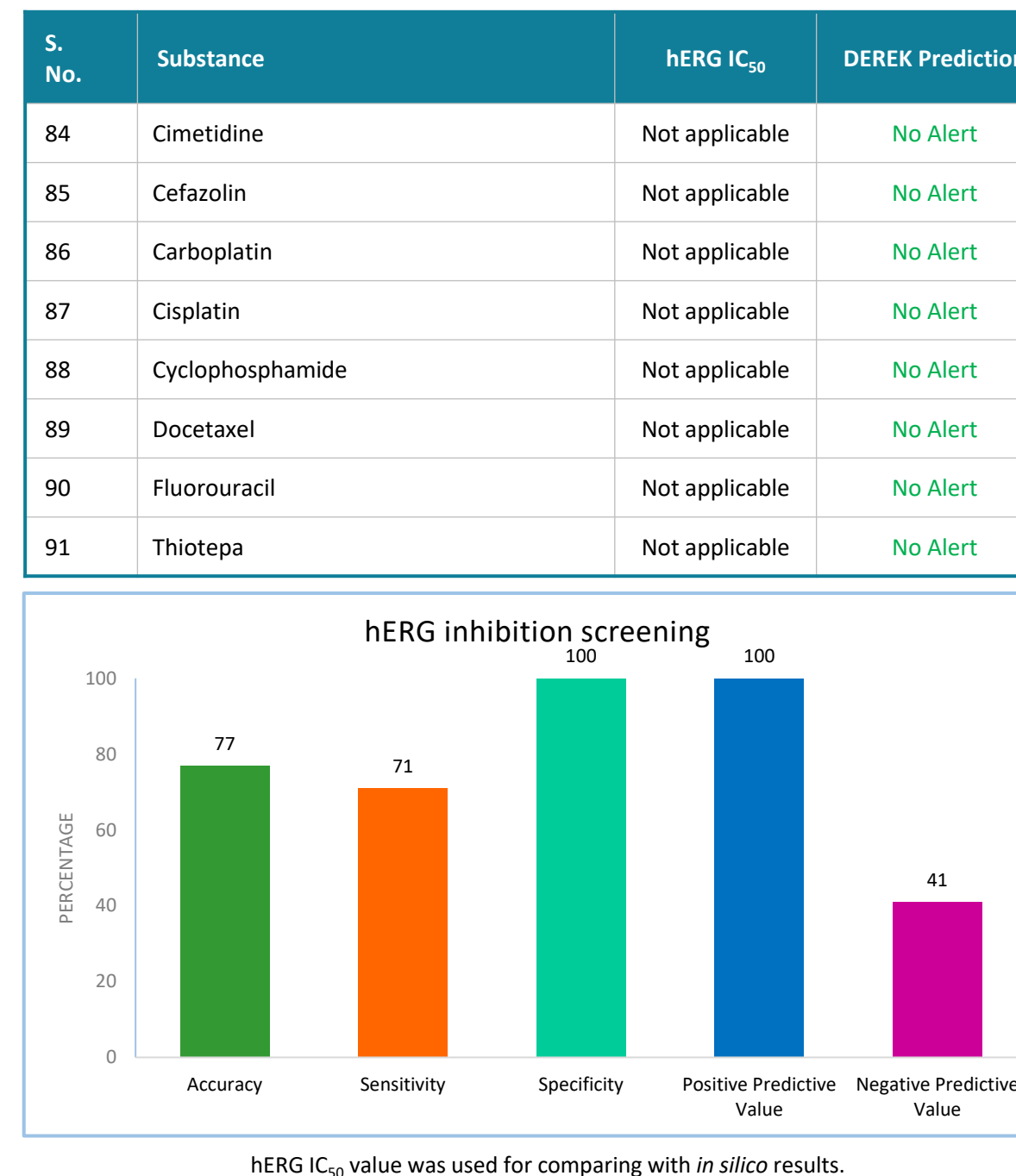
S. No.	Substances	3T3 NRU-PT*	RHE-PT†	In vivo	Human	DEREK Prediction
Phototoxic drugs						
1	Acridine HCl	PT	PT	PT	PT	No Alert
2	Amiodarone HCl	PT	No data	No data	PT	No Alert
3	Chlorpromazine HCl	PT	PT	PT	PT	PT-Probable/PA-Plausible
4	Doxycycline HCl	PT	No data	No data	PT	PT-Plausible
5	Fenofibrate	PT	PT	PT	PT	PA-Plausible
6	Furosemide	PT	NPT	NPT	PT	PT-Probable
7	Ketoprofen	PT/NPT	PT	PT	PT	PT-Plausible/PA-Probable
8	6-Methylcoumarin	PT	PT	PT	PT	PA-Probable
9	8-Methoxypsoralen	PT	PT	PT	PT	No Alert
10	Nalidixic acid	PT	No data	No data	PT	PT-Plausible
11	Norfloxacin	PT	No data	No data	PT	PT-Plausible/PA-Equivocal
12	Ofloxacin	PT	PT	PT	PT	PT-Probable/PA-Equivocal
13	Piroxicam	PT	No data	No data	PT	PT-Plausible
14	Promethazine	NPT	PT	PT	No data	PT-Probable
15	Promethazine HCl	PT	No data	No data	PT	PT-Probable
16	Tetracycline	PT	NPT	NPT	PT	PT-Plausible
17	Lomefloxacin	PT	PT	PT	No data	PT-Probable/PA-Probable
18	Demeclocycline	PT	PT	PT	No data	PT-Plausible
19	Tiaprofenic acid	PT	PT	PT	No data	PT-Probable/PA-Probable
20	Phenothiazine	PT	PT	PT	No data	PT-Plausible
21	Angelicin (Isopsoralen)	PT	PT	PT	No data	No Alert
22	Quinine HCl dihydrate	No Data	No data	No data	PT	PT-Plausible



hERG channel inhibition screening

S. No.	Substance	hERG IC ₅₀	DEREK Prediction
hERG blockers			
1	Escitalopram	2.6 uM	Plausible
2	Haloperidol	0.17uM	Plausible
3	Sertindole	0.015 uM	Probable
4	Astemizole	0.0009 uM	Probable
5	Moxifloxacin	227 uM	Equivocal
6	Droperidol	0.028 uM	Plausible
7	Chlorpromazine	1.5 uM	Plausible
8	Thioridazine	0.45 uM	Plausible
9	Clarithromycin	45 uM	No Alert
10	Chloroquine	2.5 uM	Probable
11	Domperidone	0.057 uM	Probable
12	Ondansetron	0.81 uM	Plausible
13	Sotalol	103 uM	No Alert
14	Quinidine	0.23 uM	Plausible
15	Pimozide	0.055 uM	Probable
16	Pentamidine	1.28 uM	No Alert
17	Halofantrine	0.0216 uM	Plausible
18	Azithromycin	1091 uM	No Alert
19	Vandetanib	0.4 uM	No Alert
20	Flecainide	1 uM	No Alert
21	Cisapride	0.0036 uM	Plausible
22	Dofetilide	0.01 uM	Probable
23	Paro-Aminobenzoic acid (PABA)	NPT	No data
24	Sodium Lauryl Sulphate or SDS	NPT	No data
25	Butyl Methoxydibenzylmethane	PT	NPT

S. No.	Substance	hERG IC ₅₀	DEREK Prediction
25	Amiodarone	1 uM	Plausible
26	Terfenadine	0.15 uM	Probable
27	Hydroxychloroquine	5 uM	Plausible
28	Clofazolin	13.8 uM	No Alert
29	Donepezil	0.7 uM	Plausible
30	Nilotinib	0.12 uM	No Alert
31	Paliperidone	1.2 uM	Probable
32	Tolterodine	0.013 uM	Plausible
33	Lapatinib	1.1 uM	Plausible
34	Sunitinib	0.27 uM	No alert
35	Vardenafil	30 uM	No alert
36	Nicardipine	1.3 uM	Plausible
37	Dasatinib	14.3 uM	Plausible
38	Clozapine	0.32 uM	Probable
39	Alfuzosin	134 uM	No Alert
40	Palonosetron	2 uM	Plausible
41	Lopinavir	8.6 uM	No Alert
42	Olanzapine	0.23 uM	Probable
43	Diphenhydramine	1.9 uM	Plausible
44	Risperidone	0.25 uM	Probable
45	Fluoxetine	0.7 uM	Plausible
46	Solfifenacin	0.27 uM	Plausible
47	Nefinavir	11.5 uM	Plausible
48	Eltrombopag	0.69 uM	No Alert
49	Lamotrigine	229 uM	No Alert
50	Maraviroc	42.6 uM	Plausible
51	Methylaltrexone	1606 uM	Equivocal
52	Nebivolol	0.3 uM	Plausible
53	Renzapride	27.2 uM	Equivocal
54	Sildenafil	30 uM	No alert
55	Ajalmine	5.47 uM	Equivocal
56	Apomorphine	3.11 uM	Plausible
57	Atomoxetine	8.19 uM	Plausible
58	Benperidol	0.17 uM	Plausible
59	Bupirone	6.25 uM	Plausible
60	Carvedilol	1.14 uM	Plausible
61	Cetirizine	37.2 uM	No alert
62	Chlorpheniramine maleate	9.77 uM	Plausible
63	Citalopram	3.73 uM	Plausible
64	Clofilium tosylate	0.02 uM	Plausible
65	Clomipramine	9.04 uM	Plausible
66	Clozimazole	18.77 uM	Plausible
67	Desipramine	28.05 uM	Probable
68	Diazepam	7.40 uM	No alert
69	Ritonavir	8.2 uM	No alert
70	Gefitinib	1 uM	Plausible
71	Terazosin	113.2 uM	No Alert
72	Spirolactone	23 uM	No Alert
73	Loratadine	2.3 uM	No Alert
74	Propranolol	9.9 uM	Plausible
75	Fexofenadine	65 uM	No Alert
76	Ketoconazole	1.7 uM	Plausible
hERG non-blockers			
77	Amoxicillin	Not applicable	No Alert
78	Acetylsalicylic acid	Not applicable	No Alert
79	Captopril	Not applicable	No Alert
80	Gentamicin sulphate	Not applicable	No Alert
81	Tetracycline HCl	Not applicable	No Alert
82	Methadone	Not applicable	No Alert
83	Cisapitabine	Not applicable	No Alert



Hepatotoxicity screening

S. No.	Substance	DILI concern	DEREK Prediction
Hepatotoxic drugs			
1	Mercaptopurine	Most concern	Plausible
2	Indomethacin	Most concern	Plausible
3	Phenytoin	Most concern	Probable
4	Rifampin	Most concern	No Alert
5	Abacavir	Most concern	No Alert
6	Allopurinol	Most concern	No Alert
7	Amiodarone	Most concern	Probable
8	Bicalutamide	Most concern	No Alert
9	Chlorzoxazone	Most concern	No Alert
10	Dactinomycin	Most concern	No Alert
11	Dantrolene	Most concern	Plausible
12	Diclofenac	Most concern	Equivocal
13	Diffunisal	Most concern	Probable
14	Fenoprofen	Most concern	Plausible
15	Flutamide	Most concern	Plausible
16	Hydroxyurea	Most concern	No Alert
17	Imatinib	Most concern	No Alert
18	Ketoconazole	Most concern	Plausible
19	Labetalol	Most concern	No Alert
20	Leflunomide	Most concern	No Alert
21	Mefenamic acid	Most concern	Probable
22	Methyldopa	Most concern	Plausible
23	Nefazodone	Most concern	No Alert
24	Nitrofurantoin	Most concern	Probable
25	Propylthiouracil	Most concern	Probable
26	Stavudine	Most concern	Plausible
27	Sulindac	Most concern	No Alert
28	Tizanidine	Most concern	No Alert
29	Captopril	Less concern	Plausible
30	Carbamazepine	Less concern	Probable
31	Felbamate	Most concern	Probable
32	Glimepiride	Less concern	Plausible
33	Venlafaxine	Less concern	No Alert
34	Ciprofloxacin	Most concern	Probable
35	Dacarbazine	Most concern	No Alert
36	Fosfomycin	Less concern	Plausible
37	Acetaminophen	Most concern	Probable
38	Azathioprine	Most concern	No Alert
39	Cyclophosphamide	Less concern	No Alert
40	Aciclovir	Less concern	Plausible
41	Amitriptyline	Less concern	Plausible