Impact of Physicochemical Properties on Oral Drug Dose & Hepatotoxicity

Paul Leeson

Paul Leeson Consulting Ltd leesonpd@gmail.com

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Oral Dose: The Ultimate Composite Property

Min. Effective Concentration

Volume of distribution

Absorption rate constant (rarely impacts $t_{1/2}$)

Dose interval (h)

Elimination rate constant = CL/V_{ss}

$$\text{Dose (mg/kg/day)} = \frac{(24/T).MEC.V_{ss}.(k_a - k_{el})}{F.k_a\left[\frac{1}{1-e^{-k_{el}.T}} - \frac{1}{1-e^{-k_a.T}}\right]}$$

Oral bioavailability = $F_{abs}.F_{gastrointestinal}.F_{hepatic}$

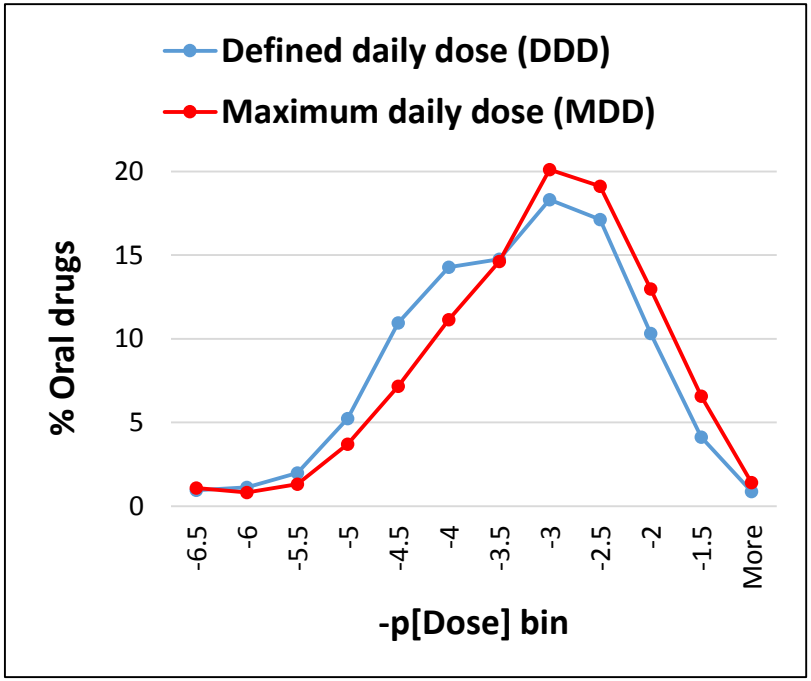
- **Human dose size & frequency prediction is a central element of lead optimisation**
  - **Dose driven by MEC/potency, F_{abs} (linear); CL, V_{ss} (exponential)**
- High dose/exposure linked to **preclinical & idiosyncratic toxicity including hepatoxicity (drug induced liver injury, DILI)**
- Dose : solubility ratio >500 mL **predicts formulation issues**

How do physicochemical properties affect: 1) oral dose & 2) DILI severity?

Human dose prediction: Grime et al, *Mol. Pharmaceutics*, **2013**, *10*, 1191; **Dose/solubility**: Butler & Dressman *J. Pharm. Sci.*, 2010, **99**, 4940: Bayliss et al, *Drug Discov. Today* 2016, **21**, 1719; **Toxicity**: Hughes et al, *Bioorg. Med. Chem. Lett.* 2008, **18**, 4872; **DILI:** Chen et al, *Drug Discov. Today*, 2016, **21**, 648; *Hepatology* 2013, **58**, 388

Oral Drug Doses: Compilation & Distribution

- Defined daily dose, **DDD (n=1261)**, WHO: '*assumed average maintenance dose per day for a drug used for its main indication in adults*.' Many recent drugs lack a DDD
- Maximum daily doses, **MDD (n=1841)**, highest dose recommended, or used for any indication. Oral drugs db updated to mid 2016 & MDDs added
- **-p[Dose]**, *not mg,* used for SAR

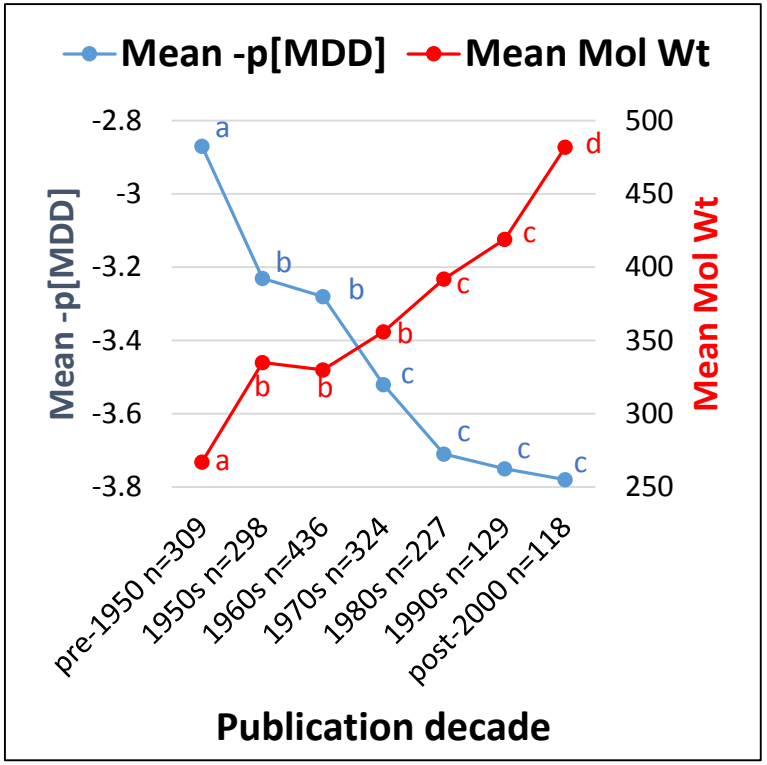


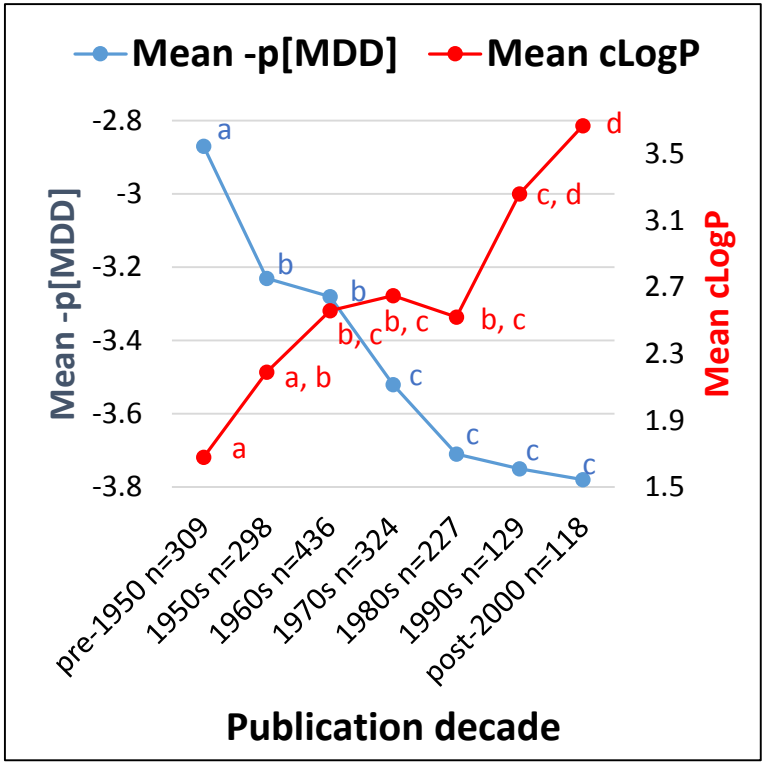
	DDD n = 1261	MDD n = 1841
Mean -p[dose]	-3.59	-3.68
90% -p[dose]	-2.30	-2.11
Median -p[dose]	-3.48	-3.23
10% -p[dose]	-4.97	-4.75
90% dose (mg)	1500	2000
Median dose (mg)	100	200
10% dose (mg)	4.1	7.5

Oral drug db: Leeson et al, *Med. Chem. Comm*. 2011, **2**, 91; **MDD**: http://www.rxlist.com/drugs/alpha_a.htm, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, http://www.drugs.com/ and other prescription drug data worldwide; Chen et al, *Hepatology* 2013, **58**, 388; Stepan et al, *Chem. Res. Toxicol.* 2011**, 24**, 1345; Matthews et al, *Curr. Drug Discov. Technol.*, 2004, **1**, 61 (exclude non oral compounds); **DDD**: Weng et al, *Oncotarget*, 2015, **6**, 17031-8; http://www.whocc.no/ddd/definition_and_general_considera/; **pDose:** Dearden et al, *SAR and QSAR Environ. Res*, 2009, **20**, 241

Oral Dose Reducing Over Time

But significantly greater increase in physical properties



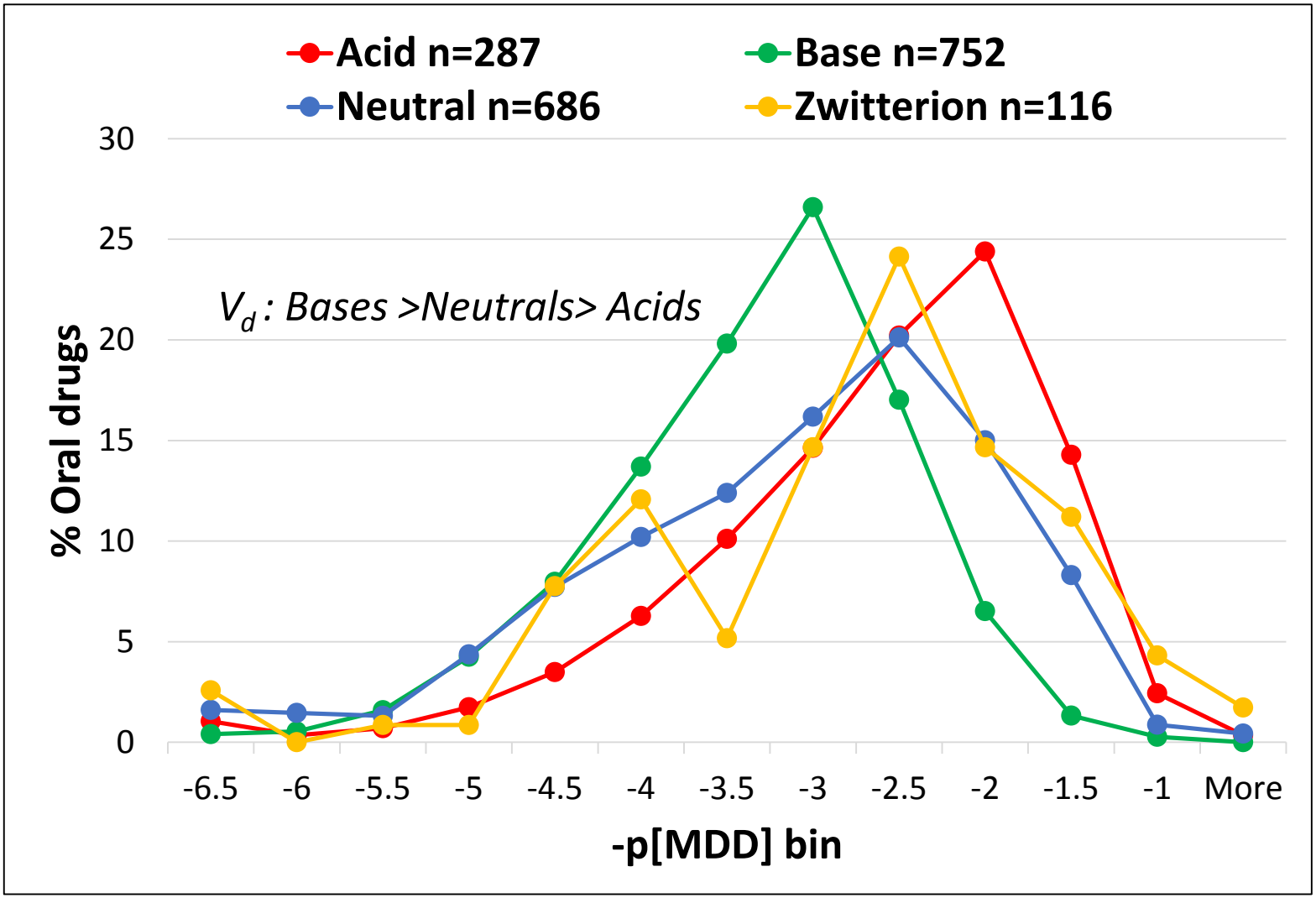


Points with different letters are statistically different (Tukey-Kramer, $p<0.05$)

- **No significant change in dose since 1970s**
- ***"Dose/property efficiency"* decreasing over time**

Oral drug physical properties vs time: Leeson & Davis *J. Med. Chem* 2004, **47**, 6338; Leeson & Springthorpe, *Nat. Rev. Drug Disc.* 2007, **6**, 881; Leeson et al, *Med. Chem. Comm*. 2011, **2**, 91

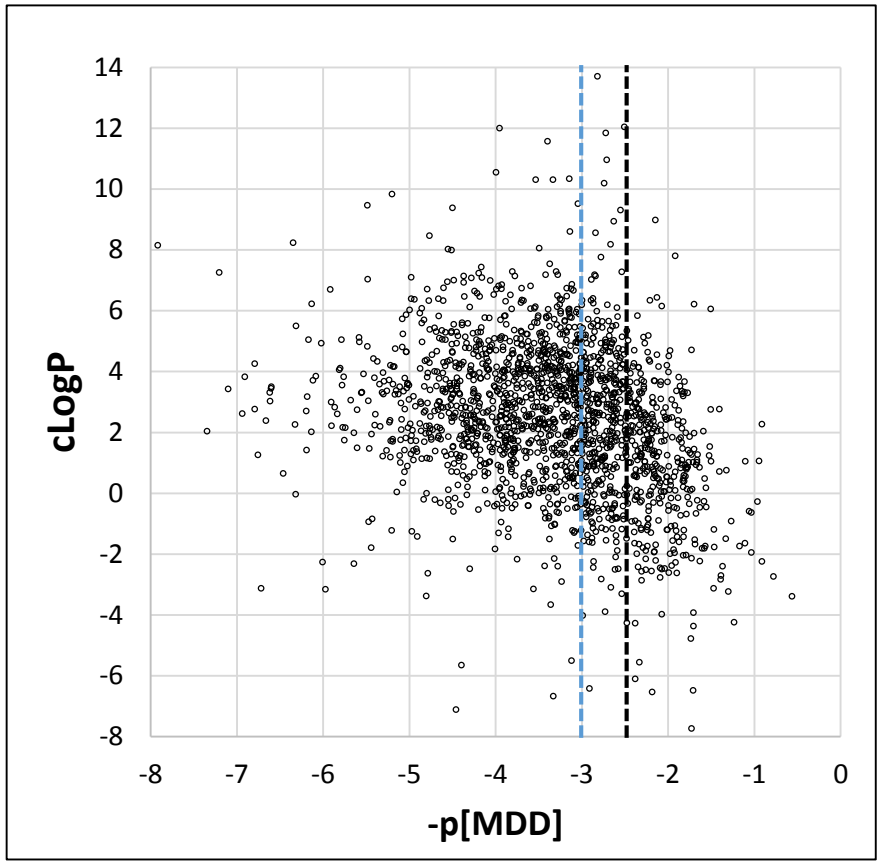
Dose & Ion Class

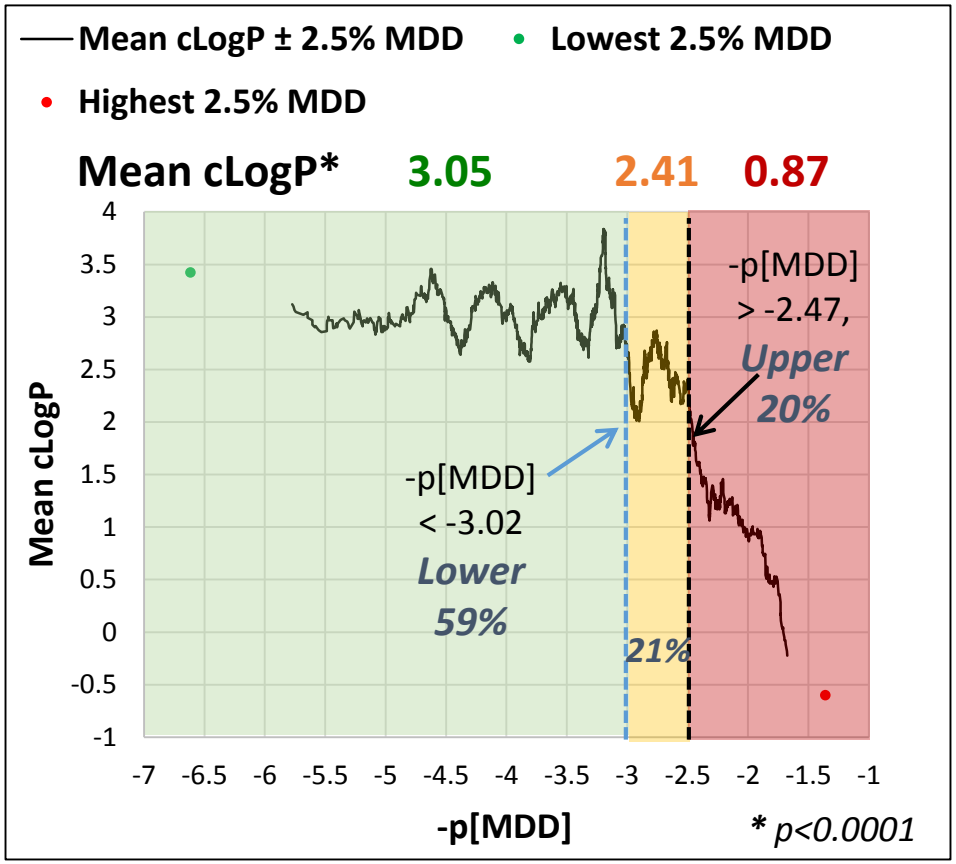


Mean –p[MDD]

A -2.91; B -3.59; N -3.36; Z -3.09 *Tukey-Kramer 0.05: A=Z; Z=N; B*

Oral Drug Lipophilicity vs -p[MDD], n=1841



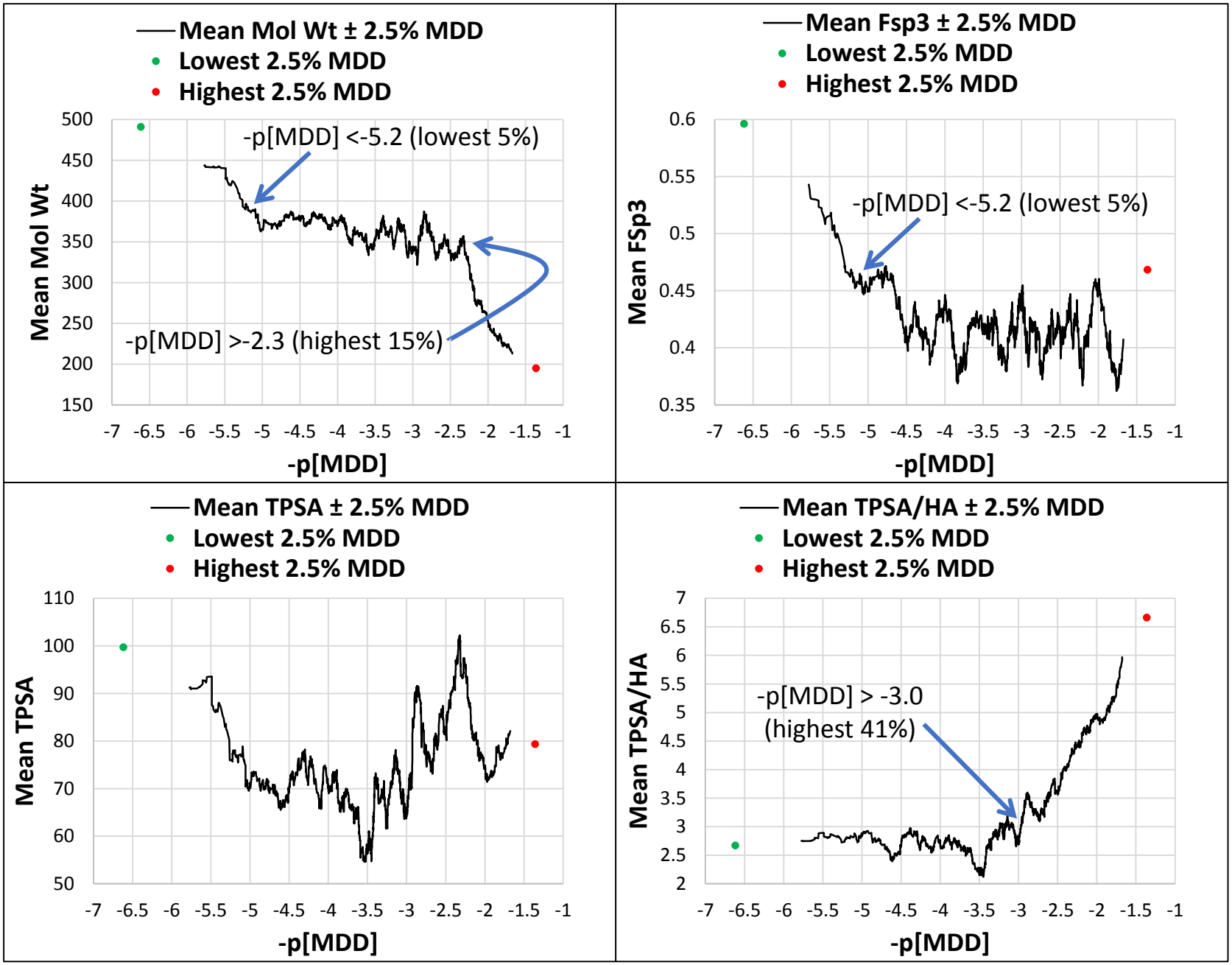


Why?

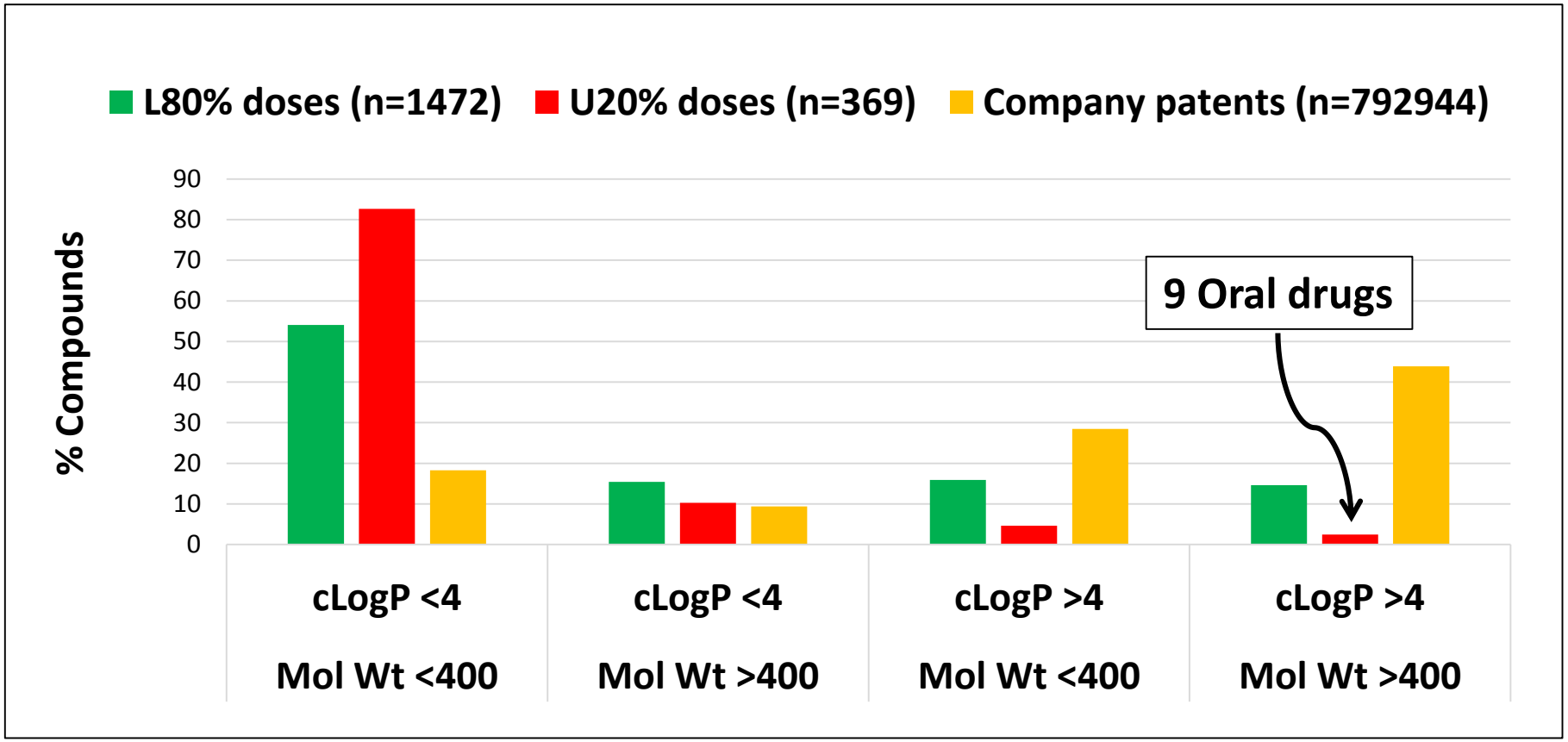
- **Increasing cLogP in oral drugs results in lower C_{free}**
- **High dose ➔ high C_{free} requires low cLogP & high solubility**
- **Increased cLogP & exposure linked to preclinical toxicity**

$[C]_{free}$: Wenlock, *Med. Chem. Comm*. 2016, **7**, 706 & 1995; **Toxicity**: Hughes et al, *Bioorg. Med. Chem. Lett.* 2008, **18**, 4872

Moving Means: Mol Wt, Fsp3, TPSA, TPSA/HA



4/400 Rule & Dose Category

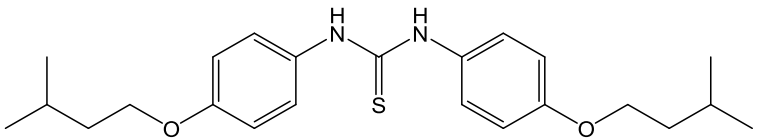


- Oral drugs with Mol Wt>400 + cLogP >4: **9.2** times more likely to have MDD in the lower 80% than in the upper 20% *(odds ratio, p <0.0001)*
- **Candidates with cLogP >4 & Mol Wt >400, the most exemplified category in patents, should be in L80% dose range**

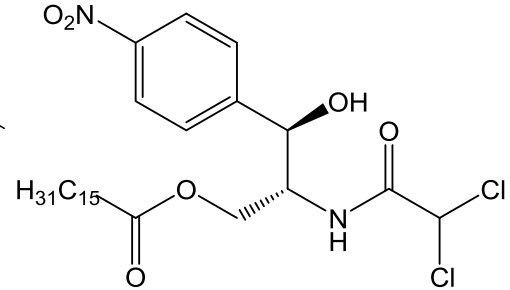
ADME 4/400 rule: Gleeson, *J. Med. Chem.*, 2008, **51**, 817
Patent data 2000-11: Leeson & St-Gallay, *Nat. Rev. Drug Disc.* 2011, **10,** 749

9/369 Oral Drugs in U20% MDD have cLogP >4 & Mol Wt >400; *3 Drugs, 3 Prodrugs & 3 Radiocontrast Agents*

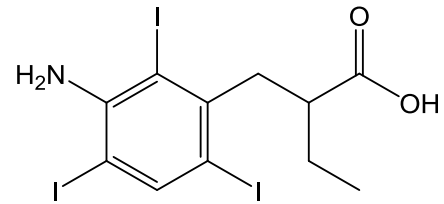
Year is publication date



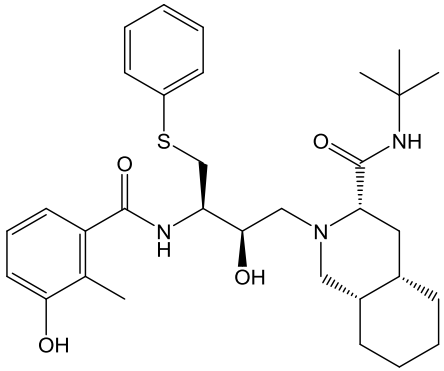
Tiocarlide; tuberculosis; 8000 mg (1953)



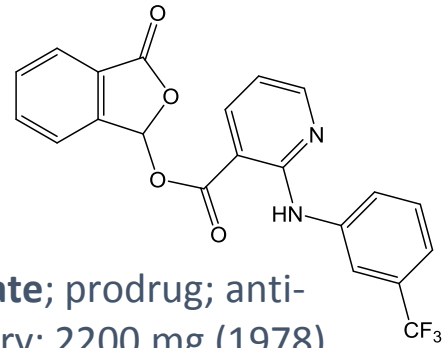
Chloramphenicol palmitate; prodrug; antibiotic; 4000 mg (1948)



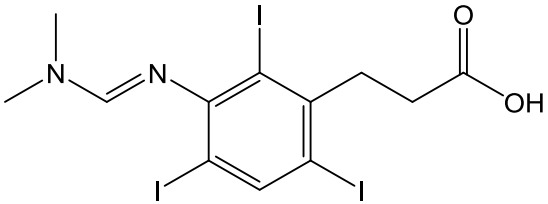
Iopanoic acid; radiocontrast medium; 6000 mg (1955)



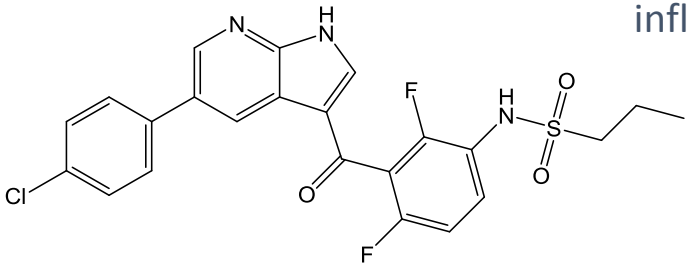
Nelfinavir; HIV; 2500 mg (1995)



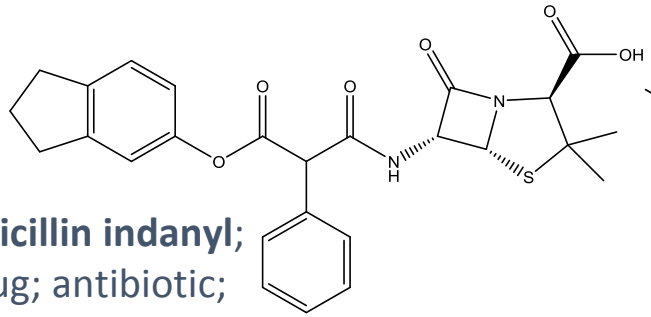
Talniflumate; prodrug; anti-inflammatory; 2200 mg (1978)



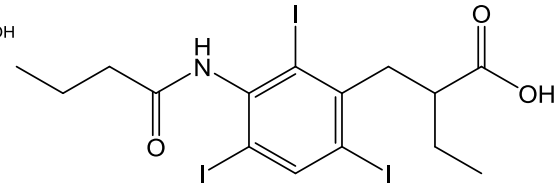
Ipodate sodium; radiocontrast medium; 6000 mg (1960)



Vemurafenib; late stage melanoma; 1920 mg (2011)



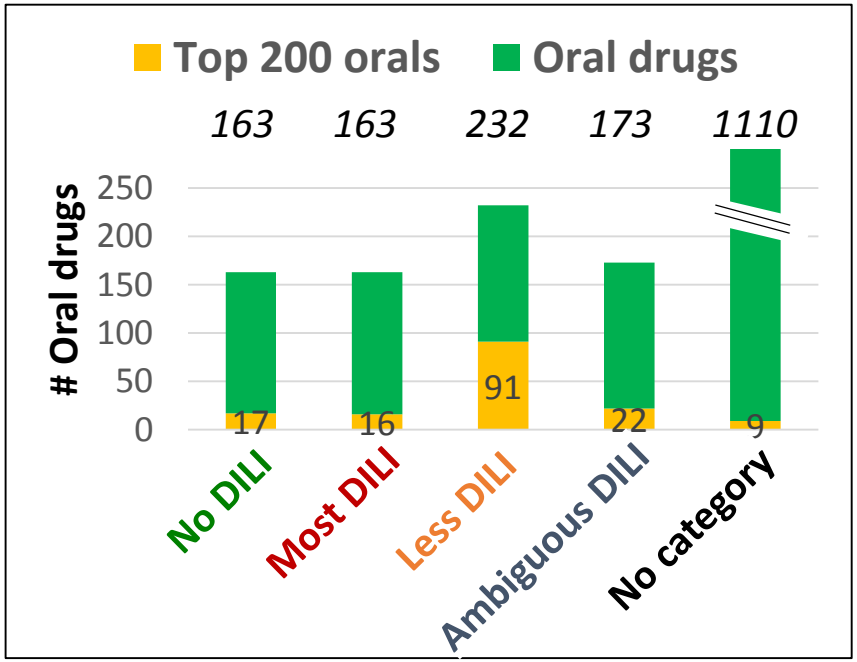
Carbenicillin indanyl; prodrug; antibiotic; 4000 mg (1969)



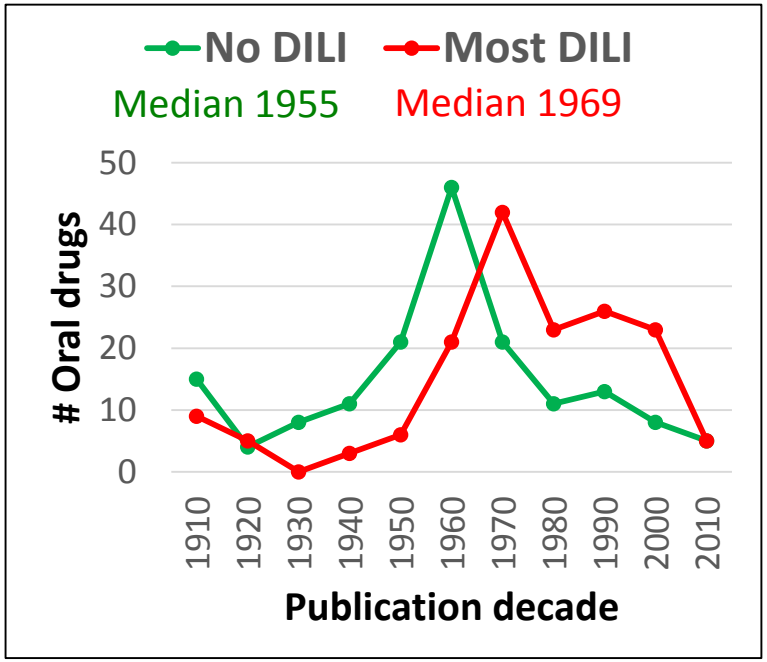
Tyropanoate sodium; radiocontrast medium; 3000 mg (1959)

Human Hepatoxicity Severity: Oral Drugs

- **116 'Most-DILI' & 48 'No-DILI' oral drugs** from FDA label
  - **Rule of 2:** highest DILI risk when **cLogP >3 & dose >100mg**
  - **QSAR**: difficult to understand physical basis; topology implicated
- **DILIrank:** 1036 FDA approved drugs with annotated DILI severity
  - **731 in oral db** (others: injectables, topicals, biologicals, mixtures)



155 of top 200 by prescription are oral

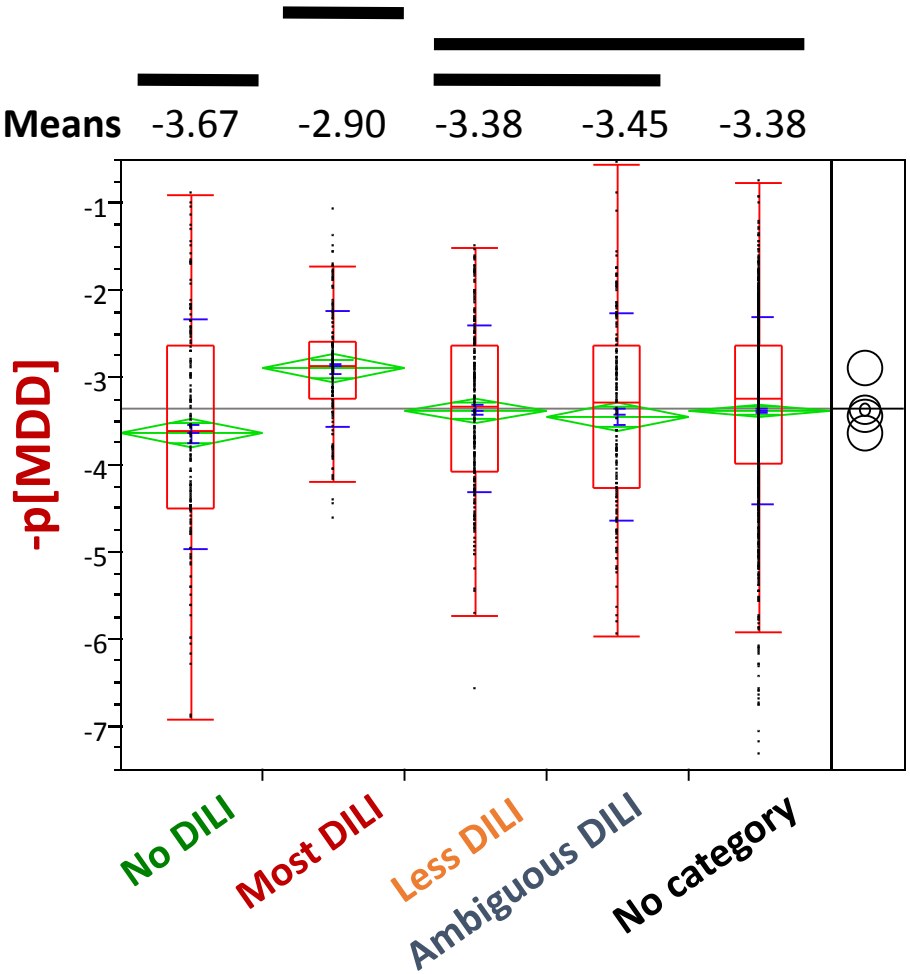


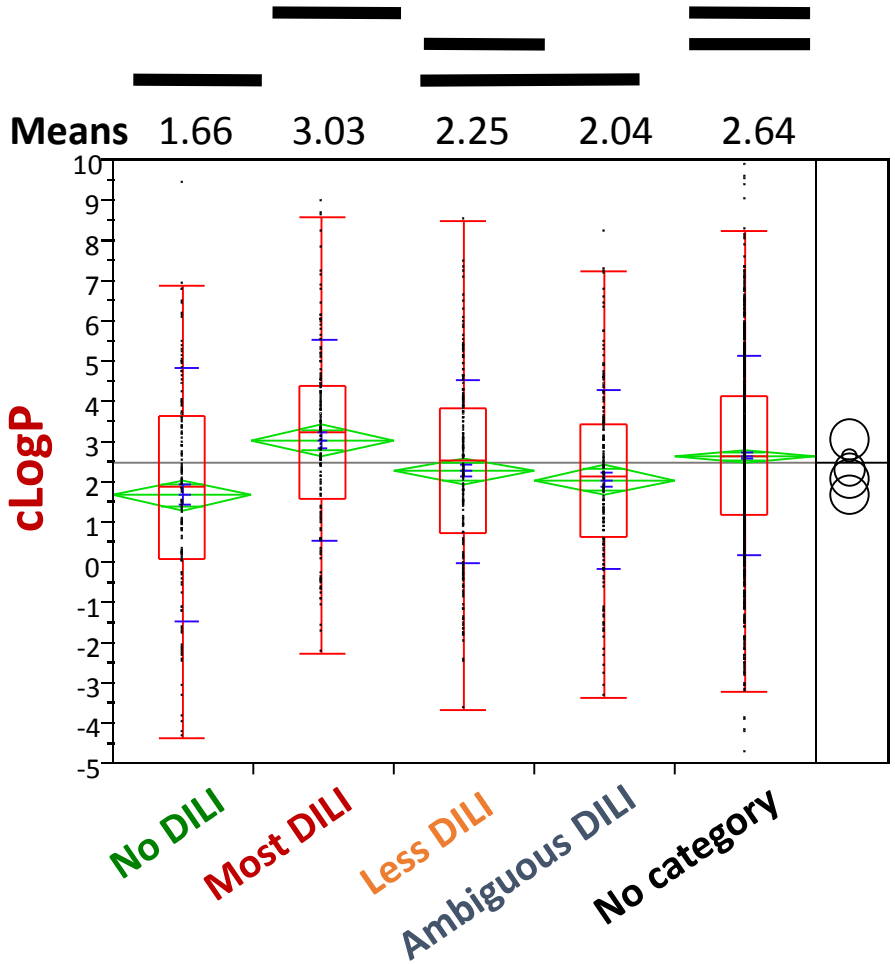
- **Reliance on historical drugs: 'No DILI' is oldest class**
- **60% of oral drug db have no DILI annotation**

Rule of 2: Chen et al, *Hepatology* 2013, **58**, 388; **QSAR/topology:** Xu et al, *J. Chem. Inf. Model.*, 2015, **55**, 2085 **DILIRank:** Chen et al, *Drug Discovery Today*, 2016, **21**, 648; **Top 200:** http://symphonyhealth.com/2015/05/top-200-drugs-of-2014/

DILI Class vs -p[MDD] & cLogP

Connected categories are not statistically different (p <0.05, Tukey-Kramer)

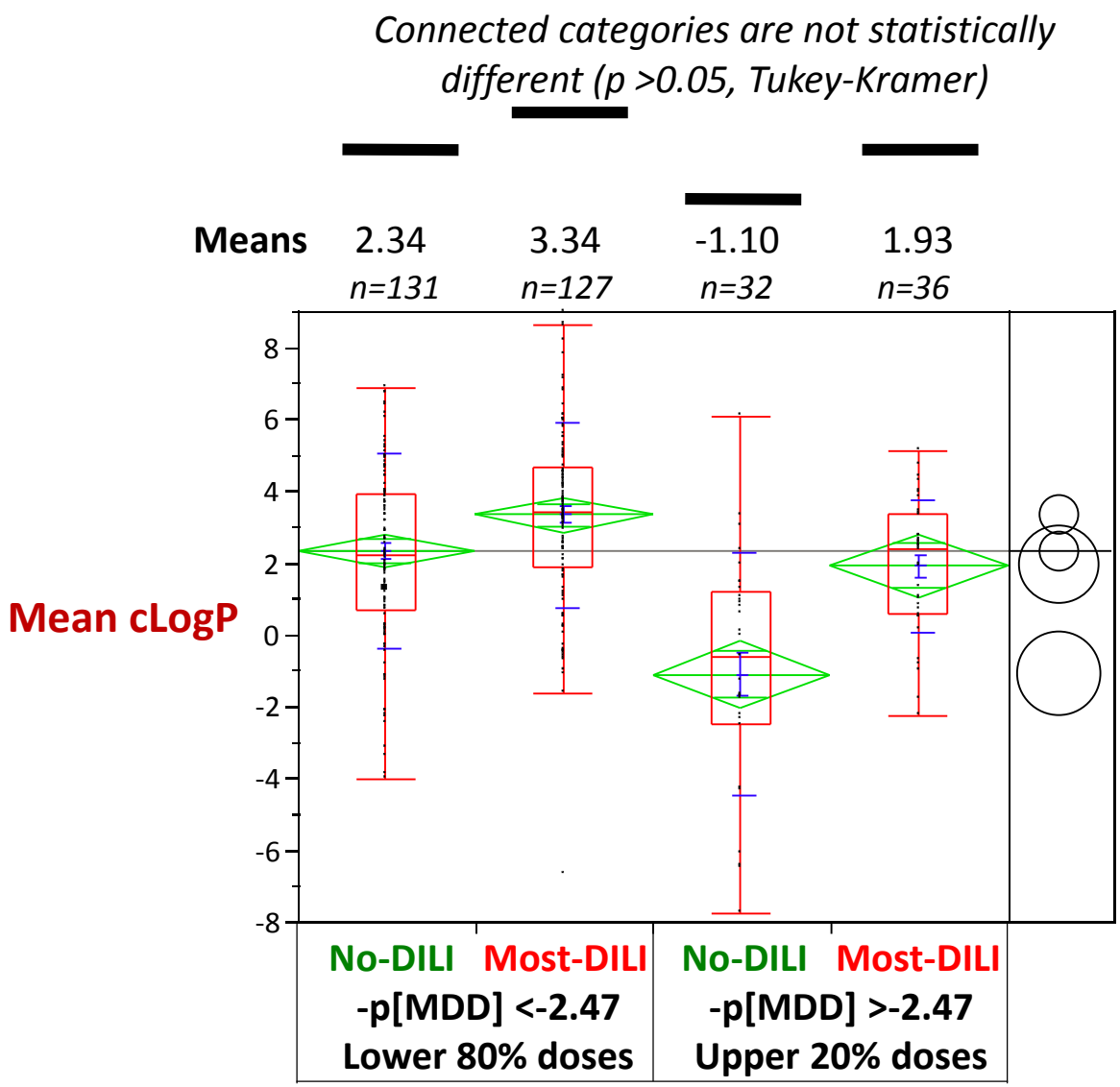




- **Most DILI < No DILI, other categories are intermediate**
- **Consistent with *rule of 2***

DILI Sensitivity to cLogP is Dose Dependent

Consistent with overall lipophilicity vs dose trend

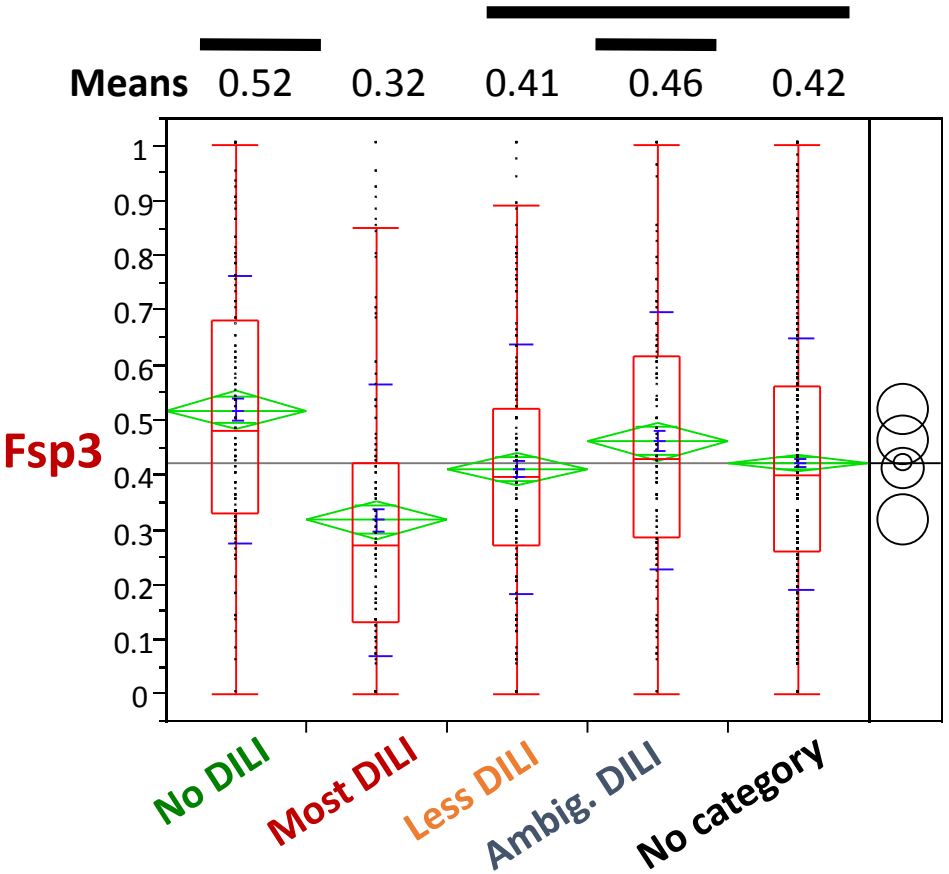


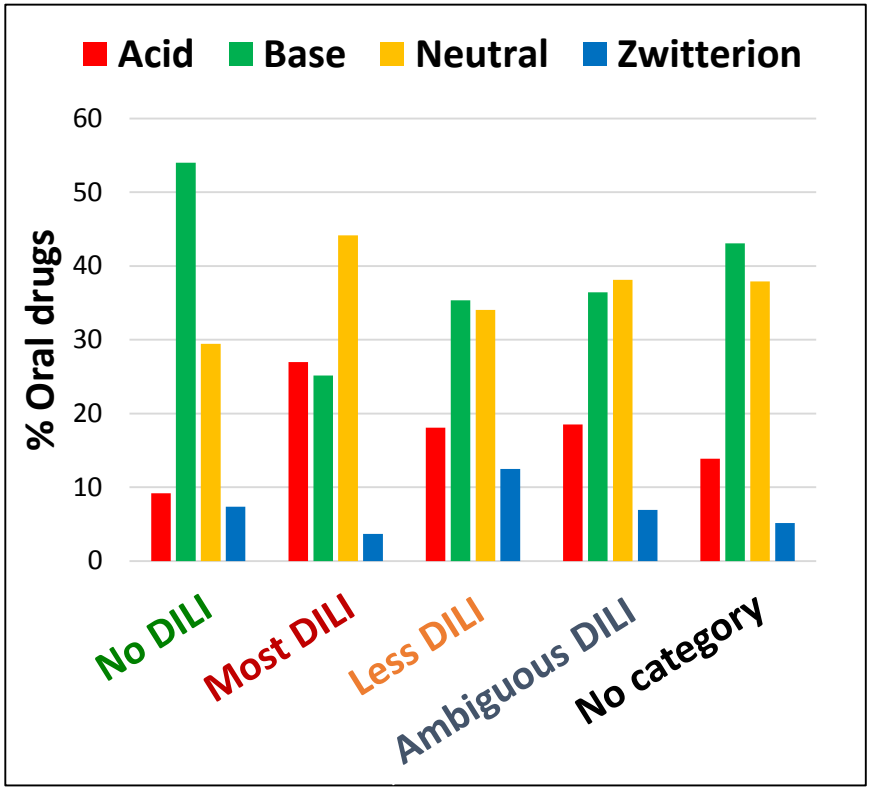
Most DILI vs No DILI

- **Lower 80% doses**
  Δ cLogP = 1.00
- **Upper 20% doses**
  Δ cLogP = 3.03

DILI Class vs Fsp3 & Ion Class

Connected categories are not statistically different (p <0.05, Tukey-Kramer)





Fsp3: Most DILI > No DILI, other categories intermediate

- **No 3D differences (rod/sphere/disc)**
- **Reactive metabolites use sp2 centres**

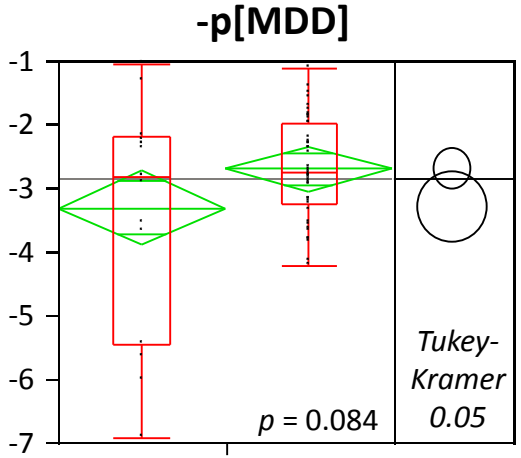
Ion class influences DILI prevalence

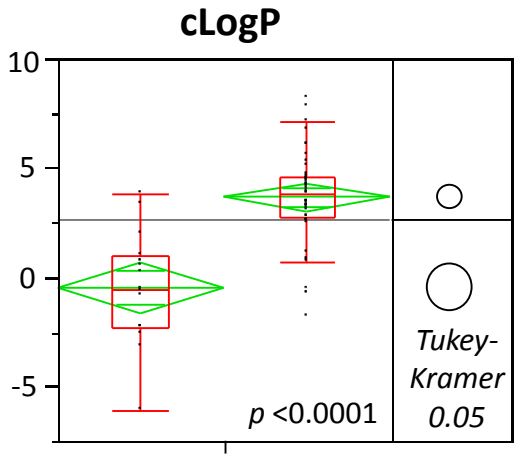
- **Neutrals: highest Most DILI; permeability?**
- **Acids: acylglucuronide formation?**
- **32/44 Most DILI acids are carboxyls**

Reactive metabolite chemistry: Stepan et al, *Chem. Res. Toxicol.* 2011, **24**, 1345

Acids: *Lipophilicity & Fsp3* more important than dose

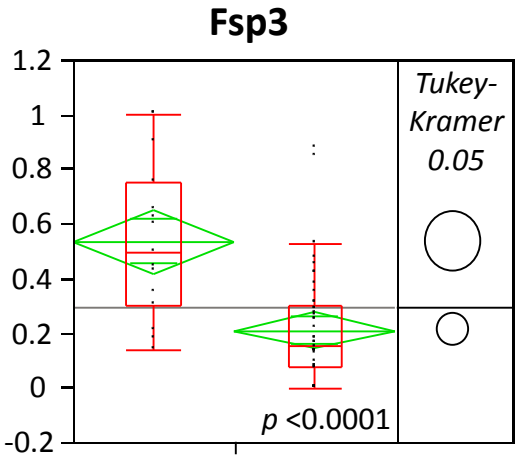
n=59: No DILI 15; Most DILI 44

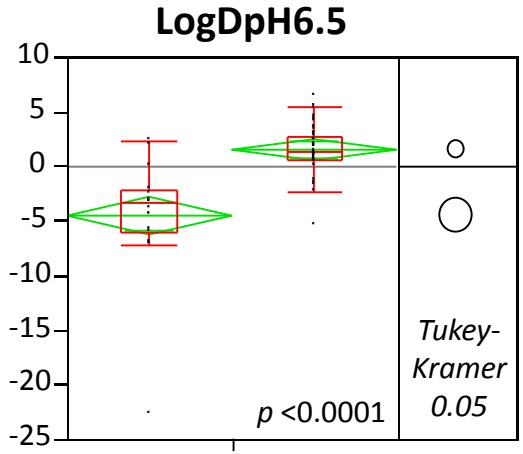




	No DILI	Most DILI
-p[MDD]	-3.30	-2.70
cLogP	-0.45	3.69

Mean values

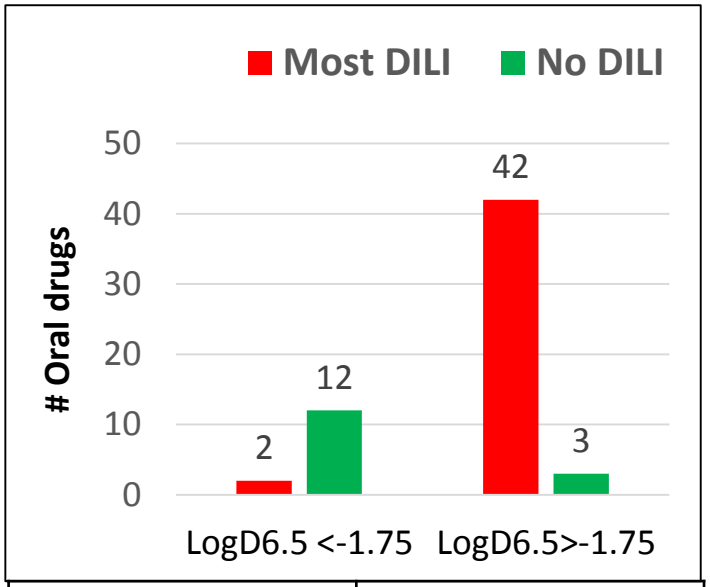




	No DILI	Most DILI
Fsp3	0.54	0.21
LogDpH6.5	-4.50	1.54

Mean values

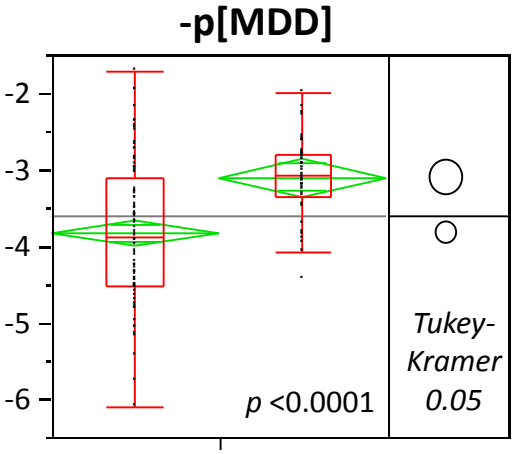
Recursive Partition



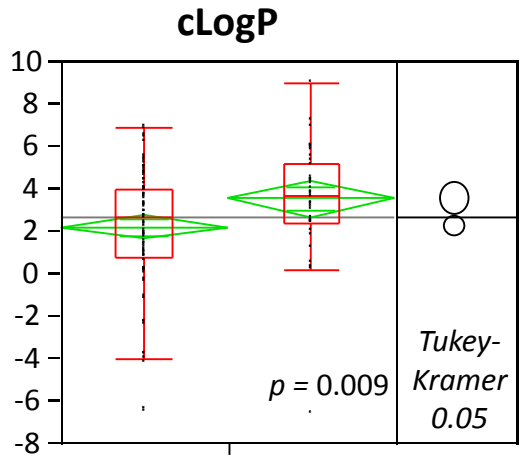
% Most	93.3
% No	80.0
Odds ratio (CI)	84.0 (12.6-562)
p	*<0.0001*

Bases: *Dose & lipophilicity* more important than Fsp3

n=129: No DILI 88; Most DILI 41

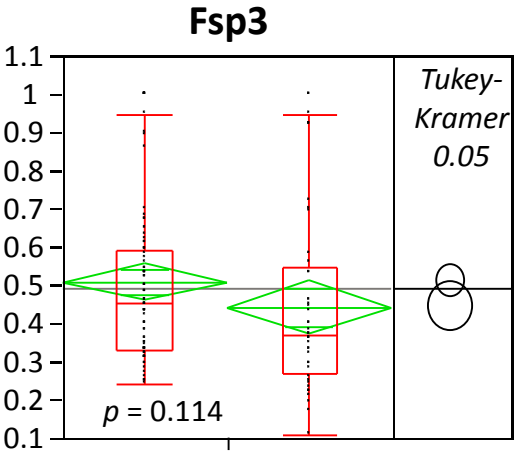


No DILI **-3.82** Most DILI **-3.09**

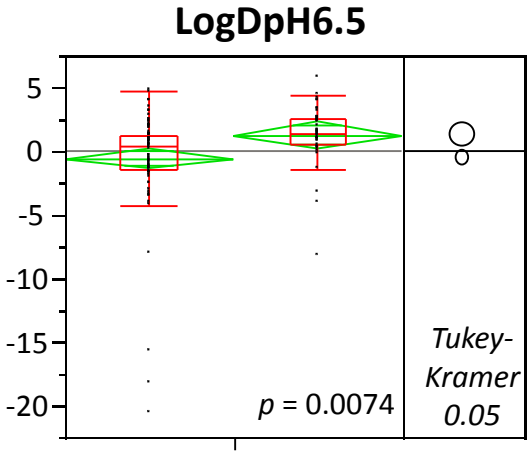


No DILI **2.19** Most DILI **3.52**

Mean values

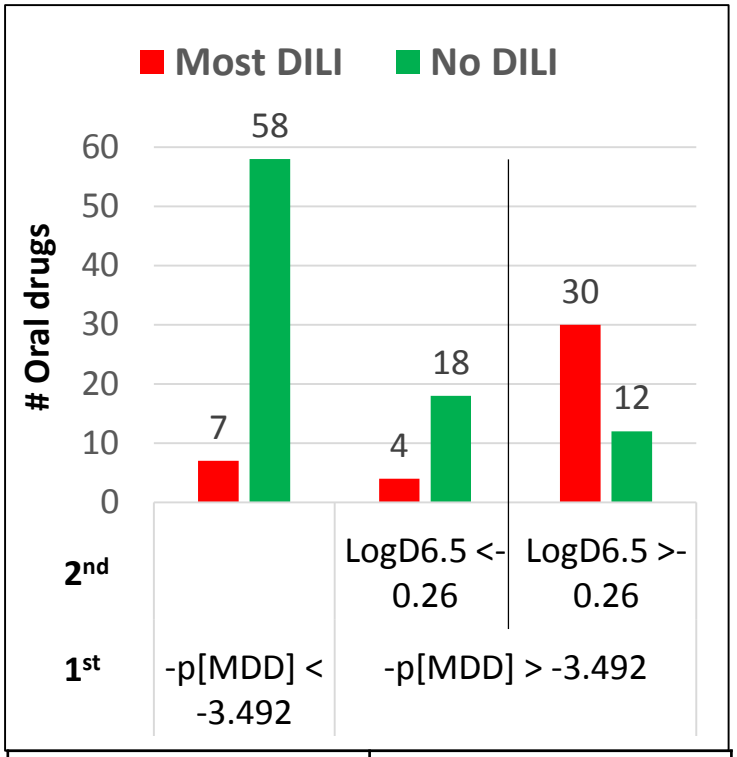


No DILI **0.51** Most DILI **0.44**



No DILI **-0.53** Mean values Most DILI **1.30**

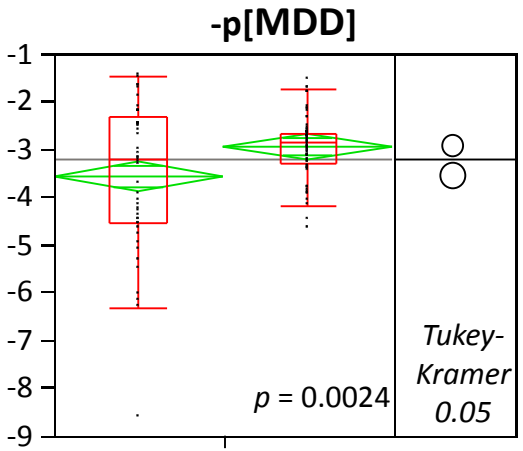
Recursive Partition



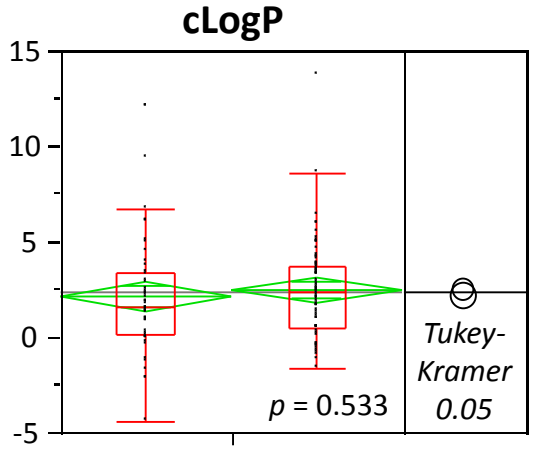
% Most	73.2
% No	86.4
Odds ratio (CI)	17.3 (6.9-43.4)
p	*<0.0001*

Neutrals: *Dose & Fsp3* more important than lipophilicity

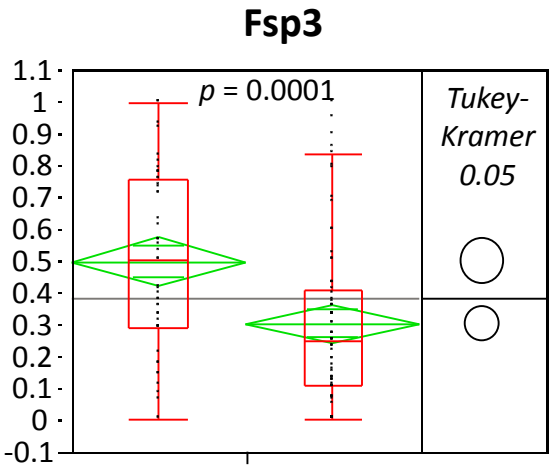
n=120: No DILI 48; Most DILI 72



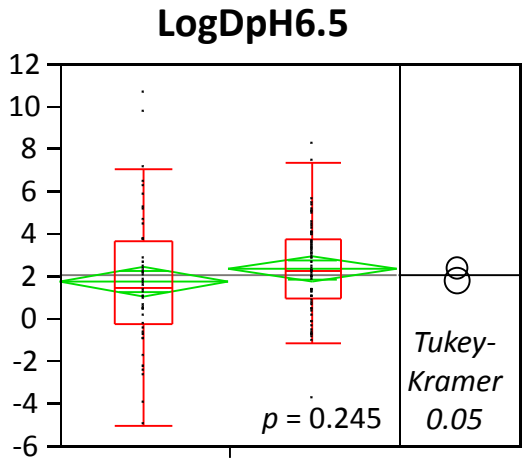
No DILI **-3.56** Most DILI **-2.94** *Mean values*



No DILI **2.18** Most DILI **2.51**

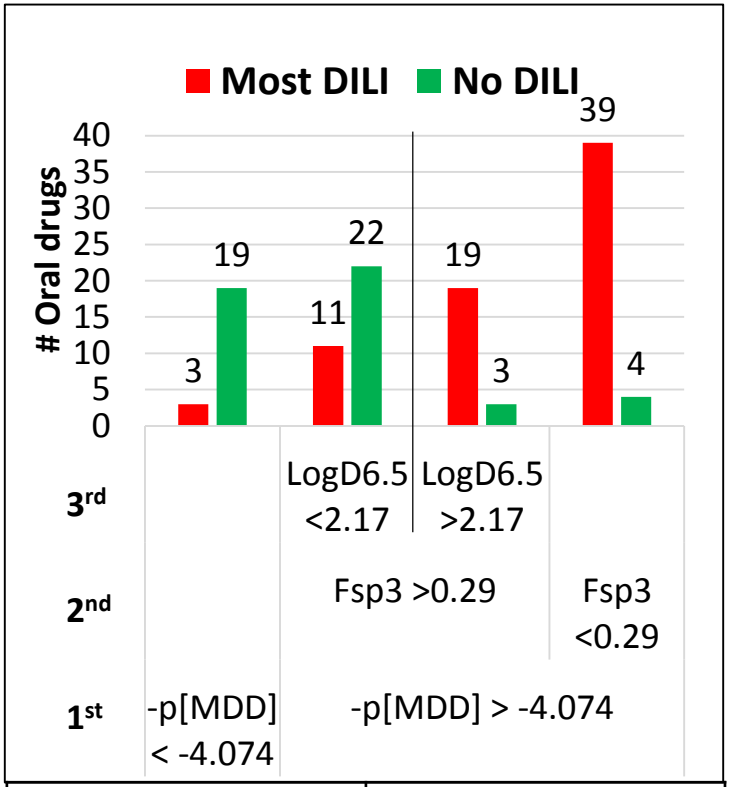


No DILI **0.50** Most DILI **0.30** *Mean values*



No DILI **1.75** Most DILI **2.32**

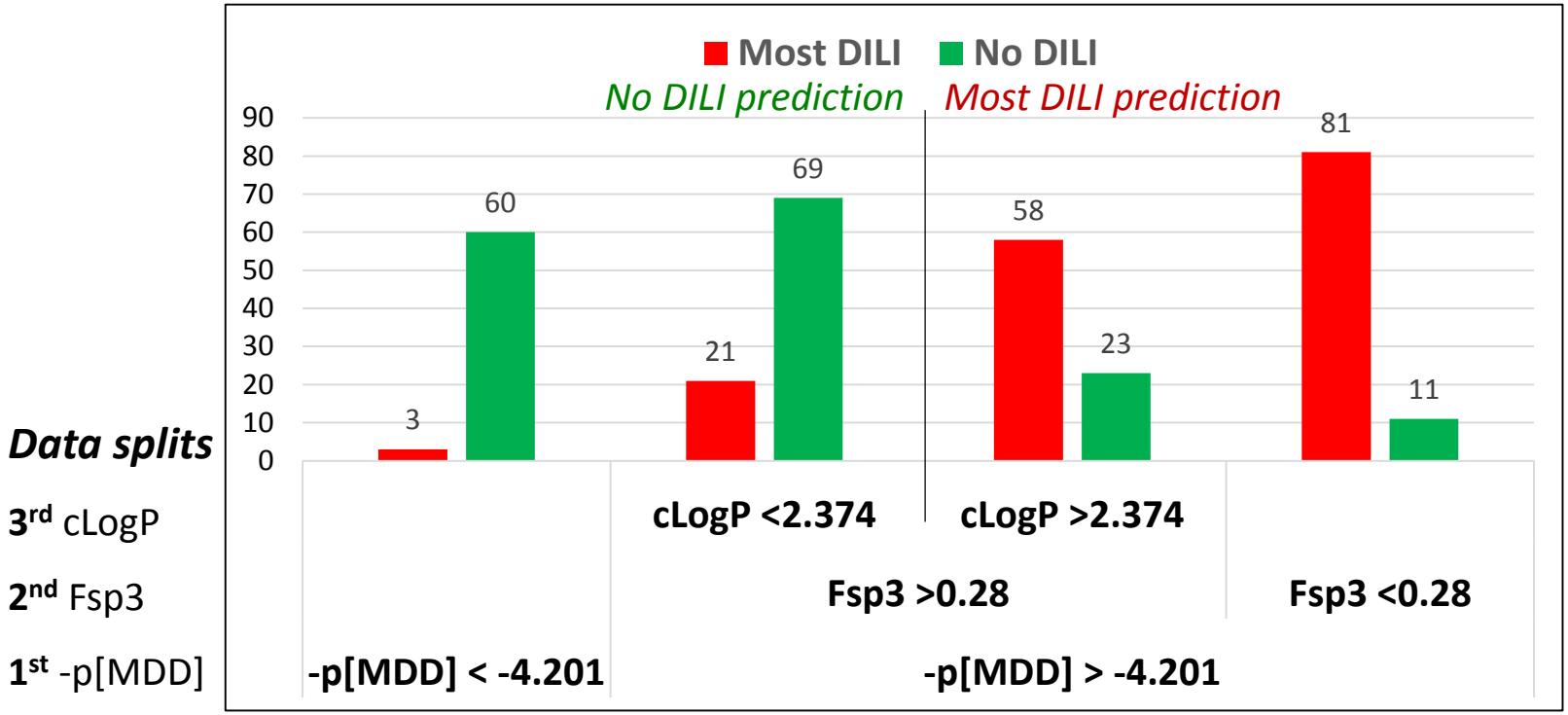
Recursive Partition



% Most	80.6
% No	85.4
Odds ratio (CI)	24.3 (9.0-65.4)
p	*<0.0001*

All Compounds: Recursive Partition

n=326: No DILI 163; Most DILI 163



% Most	85.3
% No	79.1
Odds ratio (CI)	22.0 (12.4-39.0)
p	*<0.0001*

LogDpH6.5 < or >2.2
(instead of cLogP <>2.374)

% Most	74.8
% No	89.0
Odds ratio (CI)	24.0 (13.1-43.5)
p	*<0.0001*

Model Test Set: 21 Oral Drugs Discontinued in Development Due to Human Hepatotoxicity

Compound	Ref	Max Daily Dose mg	-p[MDD]	cLogP	Fsp3	DILI prediction *'Most vs No' Model*	Fails rule of 2 (Dose >100 mg & cLogP >3)
CP-457920	a	120	-3.43	2.23	0.17	Most	No
CP-368296	a	300	-3.18	2.44	0.30	Most	No
CP-456773	a	1200	-2.53	3.38	0.45	Most	Fail
CP-085958	a	200	-3.37	4.61	0.20	Most	Fail
Zamifenacin	a	40	-4.02	5.97	0.33	Most	No
CP-422935	a	500	-2.88	6.78	0.52	Most	Fail
Darbufelone	a	10	-4.52	3.74	0.44	No	No
CP-724714	a	500	-2.97	4.64	0.19	Most	Fail
TAK-875	a	50	-4.02	4.70	0.34	Most	No
LY-2409021	a	90	-3.79	7.40	0.38	Most	No
MK-0893	a	120	-3.69	7.84	0.16	Most	Fail
ADX-10059	a	200	-3.08	4.05	0.13	Most	Fail
Telcagepant	b	560	-3.01	4.03	0.46	Most	Fail
Sitaxentan	c	300	-3.18	3.44	0.22	Most	Fail
Fialuridine	d	19	-4.29	0.02	0.56	No	No
Fiduxosin	d	120	-3.67	4.87	0.33	Most	Fail
Falnidamol	d	200	-3.29	3.82	0.33	Most	Fail
Pafuramidine	d	200	-3.26	4.79	0.10	Most	Fail
Tasosartan	d	600	-2.84	2.47	0.22	Most	No
Pralnacasan	d	1200	-2.64	2.16	0.46	No	No
Aplaviroc	d	1600	-2.56	3.92	0.55	Most	Fail
% Predicted						**86% (18/21)**	**57% (12/21)**

a. Shah et al *Tox. Sci.,* 2015, **147**, 500
b. Ho et al, *Neurology*, 2014, **83**, 958
c. https://www.gov.uk/drug-safety-update/sitaxentan-thelin-worldwide-withdrawal-from-the-market
d. Chen, et al, *Drug Discov. Today* 2016, **21**, 648

Is 'Most/No' DILI Model Useful Predictively?

- **Model distinguishes oral human drug known DILI extremes (DILIRank)**
  - *Uses well known properties: dose, Fsp3, lipophilicity, ion class*
- **Caveats:** large number of uncategorised drugs & newer drugs in changed property space Mol Wt↑, cLogP↑ vs model

DILI Class	n	Oral drugs published post-1990 (n=247) RP Model Prediction	
		n No DILI	n Most DILI
No DILI	**15**	**13**	**2**
Most DILI	**30**	**3**	**27**
Less DILI	*28*	*16*	*12*
Ambiguous DILI	*30*	*19*	*11*
No category	**144**	**62**	**82**

OK to ignore? (Top 200 = 59% 'Less DILI')

- **Majority of recent drugs have no human DILI assignment**
  - **Hepatotoxicity yet to appear?**
- **Use in conjunction with hepatotoxicity screens**
  - BSEP, reactive metabolites, covalent binding, cellular toxicities

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Summary of Mean Properties

Lower 80% vs Upper 20% MDD

Property	Mean Property Values		*Difference*	*p*
	-p[MDD] < -2.47 n = 1472 (lower 80%)	**-p[MDD] > -2.47** n = 369 (upper 20%)		
cLogP	2.88	0.88	-2.01	*<0.0001*
LogD7.4	1.59	-0.33	-1.92	*<0.0001*
PFI	5.31	2.65	-2.65	*<0.0001*
Mol Wt	366.5	276.6	-89.9	*<0.0001*
Ar ring	1.74	1.13	-0.60	*<0.0001*
Ar ring/HA	0.070	0.060	-0.010	*<0.0001*
Positive charge	0.546	0.276	-0.270	*<0.0001*
O+N/HA	0.212	0.308	0.095	*<0.0001*
OH+NH/HA	0.065	0.122	0.057	*<0.0001*
TPSA/HA	2.88	4.85	1.96	*<0.0001*
Negative charge	0.200	0.496	0.296	*<0.0001*
Chiral atoms/HA	0.063	0.0553	0.0081	*0.099*
Fsp3	0.424	0.418	0.0064	*0.642*
sp2-sp3	0.925	1.35	-0.428	*0.455*

Upper 20% < Lower 80%

Upper 20% > Lower 80%

Upper 20% = Lower 80%

Mean Physical Properties by DILI Class

	No DILI N	Most DILI M	Less DILI L	Ambiguous DILI A	No category Nc	Categories in descending property order. Groups separated by ; are statistically different *(Tukey Kramer, p<0.05)*
n	*163*	*163*	*232*	*173*	*1110*	
-p[MDD]	-3.65	-2.90	-3.38	-3.45	-3.38	M; L=Nc=A; L=A=N
cLogP	1.66	3.03	2.25	2.04	2.64	M=Nc; Nc=L; L=A=N
LogD6.5	-0.32	1.77	0.67	0.53	1.28	M=Nc; L=A; N
LogD7.4	0.063	1.76	0.80	0.64	1.46	M=Nc; L=A=N
LogP	1.40	2.82	1.90	1.76	2.40	M=Nc; L=A=N
PFI	4.07	5.15	4.35	4.03	5.02	M=Nc; L=N=A
Ar ring	1.33	1.90	1.61	1.41	1.65	M=L; Nc=L=A; L=A=N
sp2	10.2	13.8	12.7	11.8	12.8	M=Nc=L; Nc=L=A; A=N
sp2-sp3	-2.36	3.93	1.24	0.087	1.17	M=L; L=Nc=A; A=N
sp3	12.6	9.9	11.5	11.7	11.6	N=A=Nc=L; A=N=L=M
Chiral atoms	2.39	1.33	1.87	1.79	1.64	N=L=A; L=A=Nc=M
Csp3	8.85	6.38	7.71	7.93	7.96	N=Nc=A=L; A=L=M
Fsp3	0.52	0.32	0.41	0.46	0.42	N=A; A=Nc=L; M
HA	23.0	23.9	24.4	23.7	24.6	No differences
CMR	8.92	9.25	9.44	9.07	9.57	No differences
Mol Wt	330.4	345.2	351.8	338.7	352.5	No differences
RotB	4.46	4.23	4.53	4.20	4.67	No differences
HBA	3.16	3.21	3.31	3.34	2.93	No differences
HBD	1.74	1.40	1.52	1.60	1.34	No DILI differences; A=L=M=Nc
O+N	5.27	5.47	5.72	5.77	5.41	No differences
OH+NH	2.02	1.71	1.83	1.89	1.53	No DILI differences; A=L=M=Nc
TPSA	76.5	76.7	81.4	81.3	72.8	No differences

No DILI < Most DILI **No DILI > Most DILI** **No DILI = Most DILI**