Application of Current Read-Across Methodologies to the Safety Assessment of a Cosmetic Ingredient

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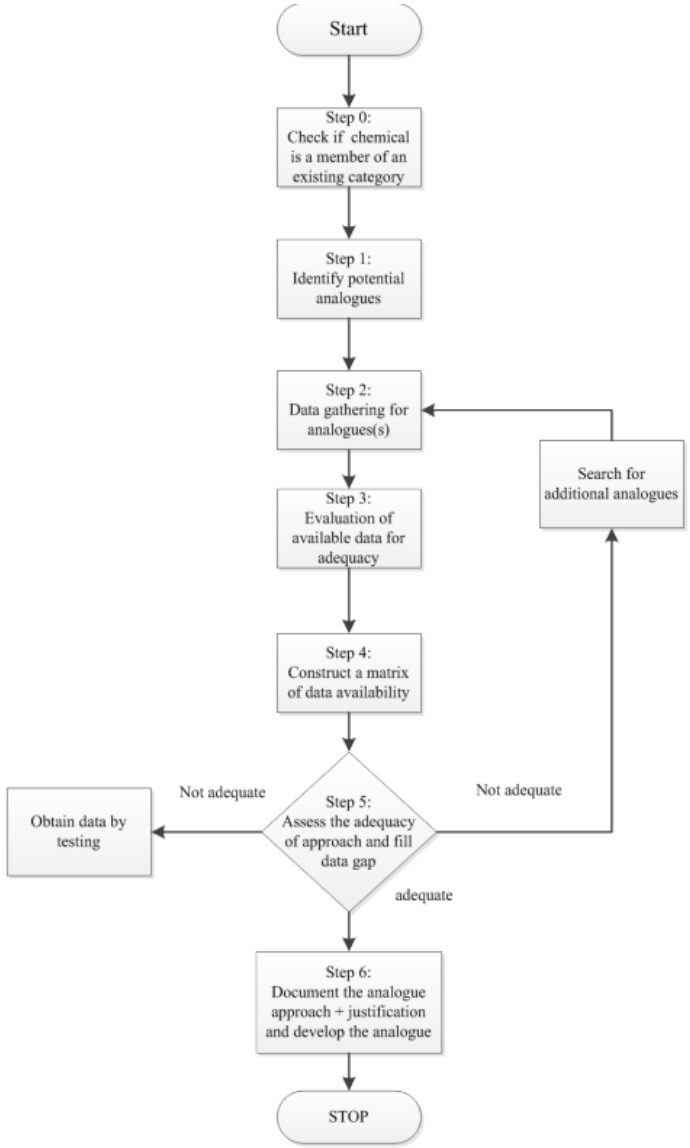
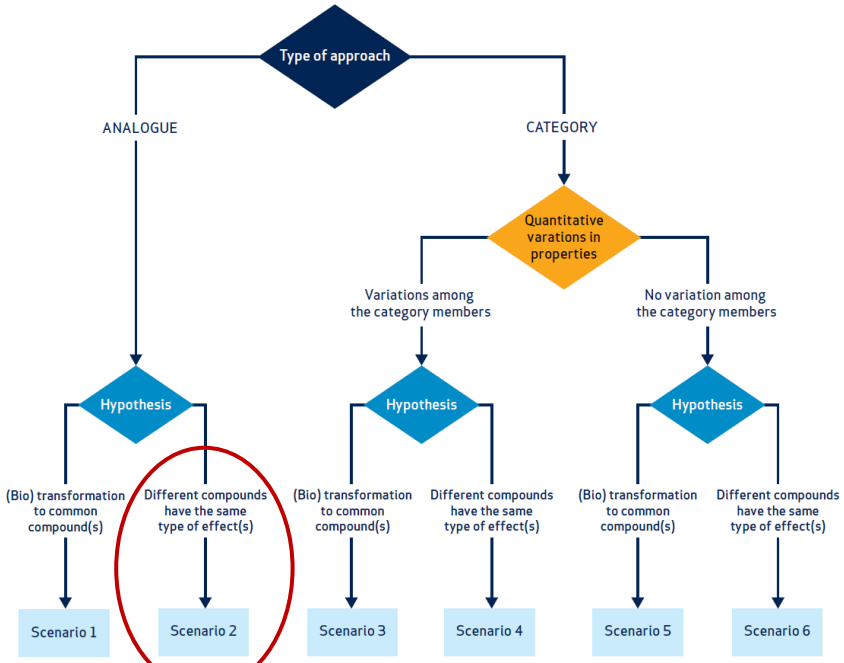
Outline

- Brief framework overview
- Description of our read-across approach for isopropyl cloprostenate
- References
- Further reading

OECD's Grouping Guidance

ECHA's Read-Across Assessment Framework





AE 2.1	Compounds the test organism is exposed to
AE 2.2	Common underlying mechanism, qualitative aspects
AE 2.3	Common underlying mechanism, quantitative aspects
AE 2.4	Exposure to other compounds than to those linked to the prediction
AE 2.5	Occurrence of other effects than covered by the hypothesis and justification

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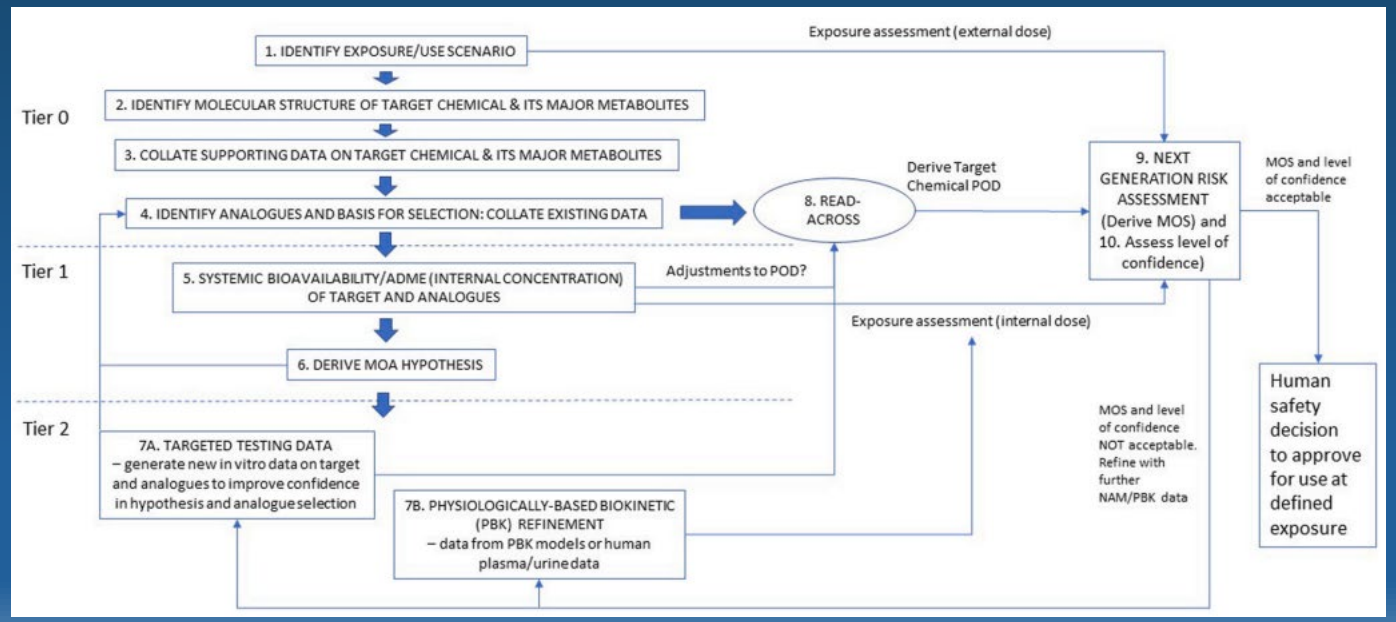
A 10-step framework for use of read-across (RAX) in next generation risk assessment (NGRA) for cosmetics safety assessment

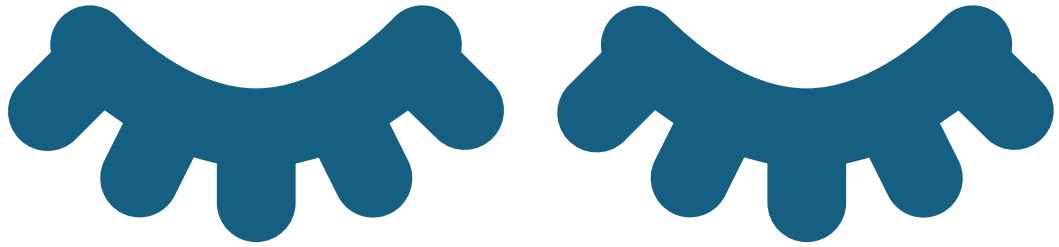
Camilla Alexander-White [a], Dagmar Bury [b], Mark Cronin [c], Matthew Dent [d], Eric Hack [e], Nicola J. Hewitt [f], Gerry Kenna [f], Jorge Naciff [g], Gladys Ouedraogo [h], Andreas Schepky [i], Catherine Mahony [j,**], Cosmetics Europe [f,*]



Principle 1: the overall goal is a human safety assessment
Principle 2: the assessment is exposure-led
Principle 3: the assessment is hypothesis-driven
Principle 4: the assessment is designed to prevent harm
Principle 5: the assessment follows an appropriate appraisal of all existing information
Principle 6: the assessment uses a tiered and iterative approach
Principle 7: the assessment uses robust and relevant methods and strategies
Principle 8: sources of uncertainty should be characterised and documented
Principle 9: the logic of the approach should be transparently and explicitly documented

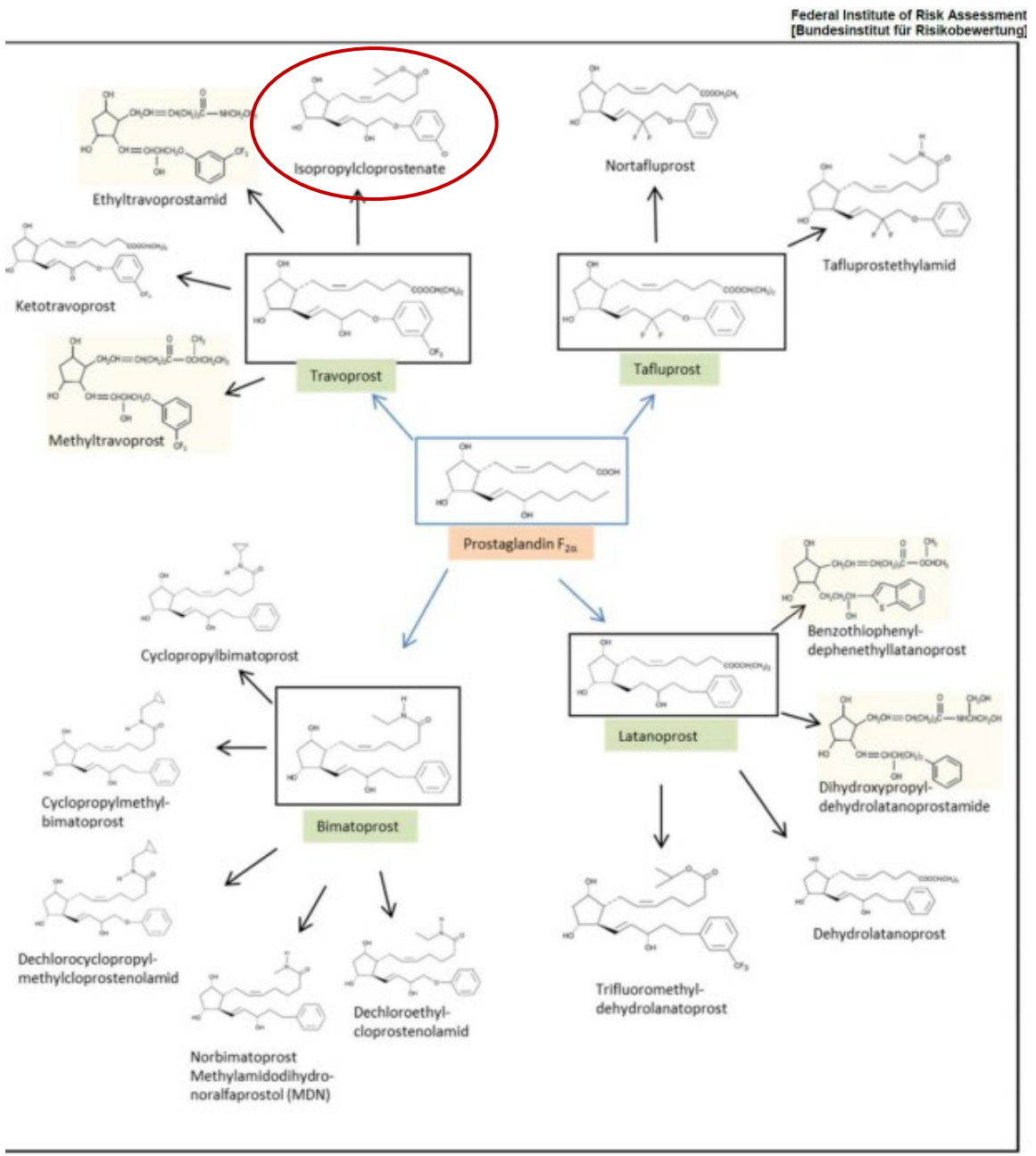
Our Approach for Isopropyl Cloprostenate (IC)

- IC is an ingredient in leave-on cosmetic eyelash serums
- The purpose of the RAX assessment is to fill the data gap for reproductive and developmental toxicity.
- Incorporated aspects of each available framework:
  - Structures and physicochemical properties
  - ADME
  - Mechanism/mode of action
  - *In silico* profiling
  - Data gathering and evaluation

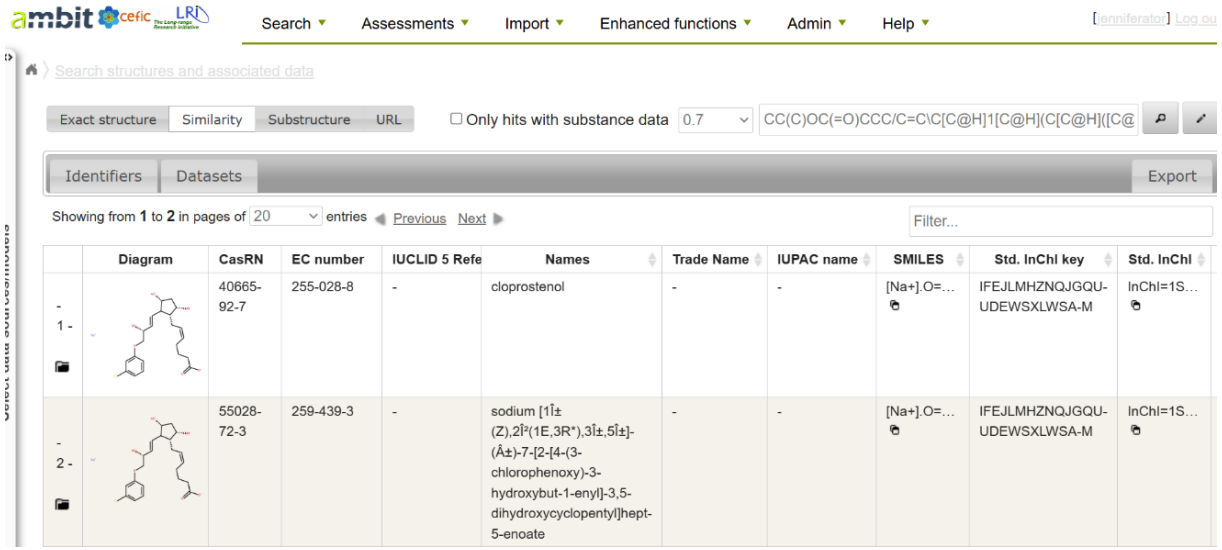


Prostaglandin F2α Analogues

- Hypothesis: IC is a PGF2α analogue, and these analogues share a common mechanism of action.
- Based on structural and mechanistic similarity, IC will have the same types of effects as other class members.

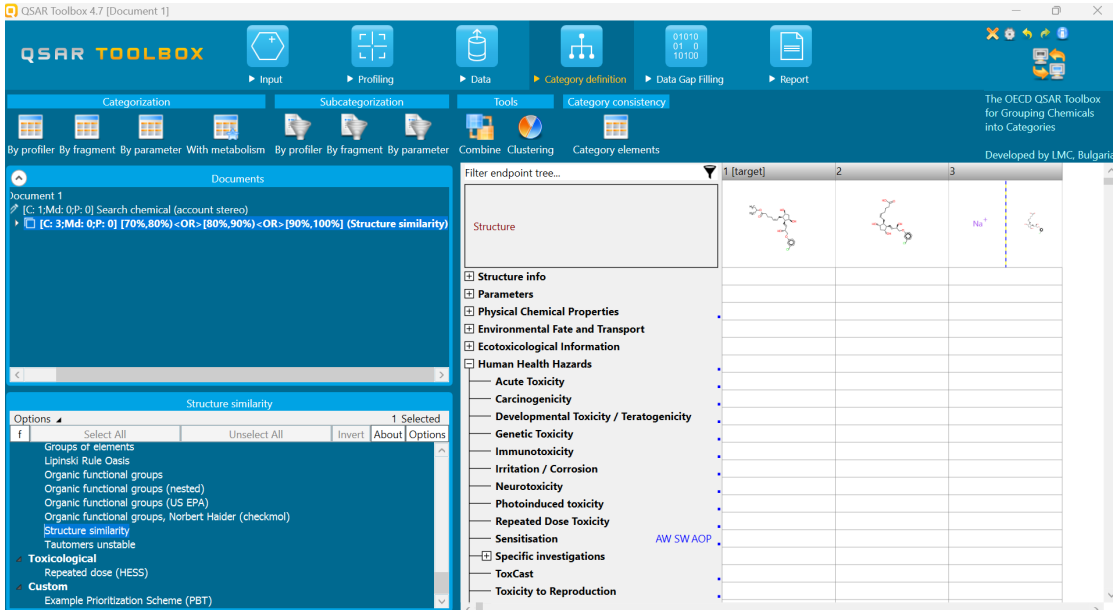


Structural Similarity Searches



AMBIT

OECD QSAR Toolbox

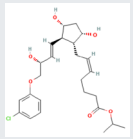
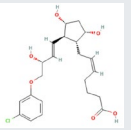
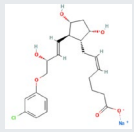
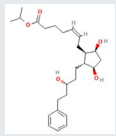
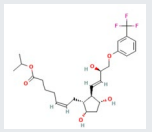
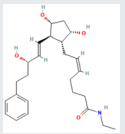


Initial Structural Similarity Analysis

Structural Similarity Analysis Between IC and Analogue Candidates

Name	SMILES	ChemMine	OECD QSAR Toolbox
Isopropyl Cloprostenate	CC(C)OC(=O)CCC\C=C/C[C@H]1[C@@H](O)C[C@@H](O)[C@@H]1\C=C\[C@@H](O)COc2cccc(Cl)c2	-	-
Cloprostenol	C1[C@@H]([C@@H]([C@H]([C@@H]1O)/C=C/[C@H](COC2=CC(=CC=C2)Cl)O)C/C=C\CCCC(=O)O)O	AP Tanimoto: 0.725 MCS Tanimoto: 0.906 MCS Size: 29 MCS Min: 1.000 MCS Max: 0.906	Tanimoto (Jaccard): 0.743
Sodium cloprostenol	C1[C@@H]([C@@H]([C@H]([C@@H]1O)/C=C/[C@H](COC2=CC(=CC=C2)Cl)O)C/C=C\CCCC(=O)[O-])O.[Na+]	AP Tanimoto: 0.725 MCS Tanimoto: 0.879 MCS Size: 29 MCS Min: 0.967 MCS Max: 0.906	Tanimoto (Jaccard): 0.771
Latanoprost	CC(C)OC(=O)CCC\C=C/C[C@H]1[C@@H](O)C[C@@H](O)[C@@H]1CC[C@@H](O)CCc2ccccc2	AP Tanimoto: 0.623 MCS Tanimoto: 0.465 MCS Size: 20 MCS Min: 0.645 MCS Max: 0.625	Tanimoto (Jaccard): 0.537
Travoprost	CC(C)OC(=O)CCC\C=C/C[C@H]1[C@@H](O)C[C@@H](O)[C@@H]1\C=C\[C@@H](O)COc2cccc(c2)C(F)(F)F	AP Tanimoto: 0.742 MCS Tanimoto: 0.861 MCS Size: 31 MCS Min: 0.969 MCS Max: 0.886	Tanimoto (Jaccard): 0.811
Bimatoprost	CCNC(=O)CCC\C=C/C[C@H]1[C@@H](O)C[C@@H](O)[C@@H]1\C=C\[C@@H](O)CCc2ccccc2	AP Tanimoto: 0.549 MCS Tanimoto: 0.476 MCS Size: 20 MCS Min: 0.667 MCS Max: 0.625	Tanimoto (Jaccard): 0.512

Physiochemical Properties and General Structural Features of IC and Analogue Candidates

Property	Isopropyl Cloprostenate	Cloprostenol	Sodium Cloprostenol	Latanoprost	Travoprost	Bimatoprost
CAS	157283-66-4	40665-92-7 / 54276-21-0	55028-72-3 / 62561-03-9	130209-82-4	157283-68-6	155206-00-1
Molecular formula	$C_{25}H_{35}ClO_6$	$C_{22}H_{29}ClO_6$	$C_{22}H_{28}ClNaO_6$	$C_{26}H_{40}O_5$	$C_{26}H_{35}F_3O_6$	$C_{25}H_{37}NO_4$
Structure						
MW	467.0	424.9	446.9	432.6	500.6	415.6
Charges	0	0	0	0	0	0
Water solubility	0.047 mg/L (calculated)	68 mg/L (calculated)	10 mg/L	12.9 mg/L	7.59 mg/L	18.7 mg/L
Partition coefficient	5.15 (calculated)	2.50 (calculated)	0.715 (calculated)	3.98	4.6	3.2
Functional Groups						
RNH_2	0	0	0	0	0	0
R_2NH	0	0	0	0	0	0
R_3N	0	0	0	0	0	0
RCONHR’	0	0	0	0	0	1
$ROPO_3$	0	0	0	0	0	0
ROH	3	3	3	3	3	3
RCHO	0	0	0	0	0	0
RCOR	0	0	0	0	0	0
RCOOH	0	1	0	0	0	0
RCOOR	1	0	1	1	1	0
ROR	1	1	1	0	1	0
RCCH	0	0	0	0	0	0
RCN	0	0	0	0	0	0
Rings	2	2	2	2	2	2
Aromatic	1	1	1	1	1	1

ADME Considerations

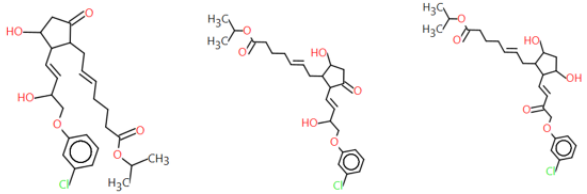
Toxicokinetic Properties of IC and Analogue Candidates				
	Property			
Substance	**Absorption**	**Distribution**	**Metabolism**	**Excretion**
Isopropyl cloprostenate	Displays low dermal absorption.	Data gap	Hydrolyzed to cloprostenol via esterases. OECD QSAR Toolbox predicted 11 hepatic metabolites, 7 skin metabolites, and 10 additional metabolites for IC, all in rats. Predicted skin metabolites include isopropyl alcohol, cloprostenol, and both hydrolyzed and non-hydrolyzed oxidation products.	Data gap
Cloprostenol / Sodium cloprostenol	Data gap	In pigs and cows, the highest levels were measured in the kidneys and liver after a single i.m. injection.	Undergoes β-oxidation following i.m. injection. The main metabolite in most species (e.g., rat, pigs, cattle) is the tetranor acid. OECD QSAR Toolbox identified 11 hepatic metabolites, 3 skin metabolites (all of which were also identified for IC), and 5 additional metabolites, all in rats.	Primarily urinary (60%) following subcutaneous injection. Terminal half-life of elimination is approx. 3 hours in cows and pigs after i.m. injection.
Latanoprost	C_{max} = 53 pg/mL and t_{max} = 5 min for the acid after a 2.3 µg ocular dose of the ester (humans).	V_d = 0.16 L/kg in humans; up to 90% plasma protein binding. No evidence of accumulation in plasma over one year.	Hydrolyzed by corneal esterases. Also completely hydrolyzed in plasma following i.v. injection. The acid undergoes rapid fatty acid β-oxidation in the liver to dinor and tetranor metabolites, which are likely glucuronidated.	Rapidly eliminated, primarily in the urine, after i.v. and topical administration. Plasma elimination half-life is approx. 16 minutes for both routes of exposure (humans).
Travoprost	Very low systemic exposure to the ester after repeated ocular administration. C_{max} = 25 pg/mL and t_{max} = 15 min for the acid after a single topical dose of the ester (2 µg) (all human data).	Approx. 80% plasma protein binding in human plasma. No evidence of accumulation over 7 days. In pregnant and non-pregnant rats administered radiolabeled travoprost by s.c. injection, the highest levels were measured in the kidneys, liver, and lungs. Levels in fetal tissues, primarily liver and lung, are about 2-4% of maternal plasma levels.	Rapidly hydrolyzed by corneal and plasma esterases. The acid is rapidly metabolized via β-oxidation, oxidation of the 15-hydroxy group, and reduction of the 13,14 double bond to dinor and tetranor metabolites.	Rapidly eliminated from plasma after ocular exposure in humans. In rats, excreted primarily in feces.
Bimatoprost	Absorbed following ocular exposure. C_{max} = 0.07 ng/mL and t_{max} = 0.1 hr for bimatoprost following a single ocular dose in humans, with no evidence of accumulation over 14 days when given once per day.	Vd = 0.67 L/kg. The highest levels of bimatoprost were measured in the GI tract, liver, kidneys, and urinary bladder after a single i.v. dose in rats. Plasma protein binding in humans is about 88%.	Bimatoprost is not metabolized in human blood, and the acid metabolite was not detected in human blood after a single ocular dose of bimatoprost. The acid metabolite is detectable in human blood after a single i.v. injection. Undergoes deamidation and glucuronidation in human liver slices. Incubation of bimatoprost with human hepatic CYP3A4/5 yields hydroxylated metabolites.	Rapidly eliminated following i.v. injection, with an elimination half-life of 45 minutes. Primarily renal elimination.

*Mathematical models (Kp and Jmax) predict low dermal absorption for both IC and travoprost.

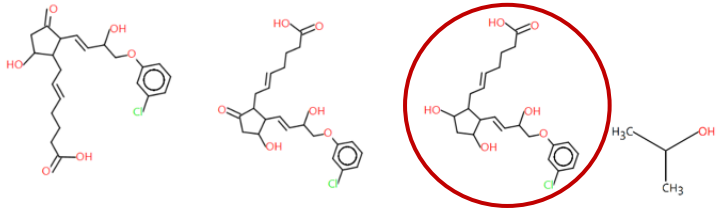
Predicted Skin Metabolites – OECD QSAR Toolbox

IC

Oxidation Products

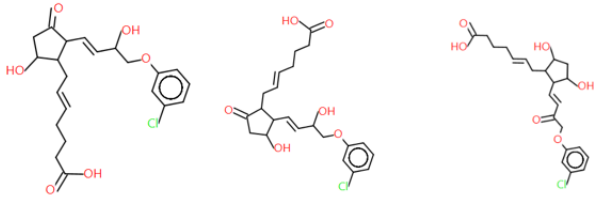


Hydrolysis Products (with or without additional oxidation)



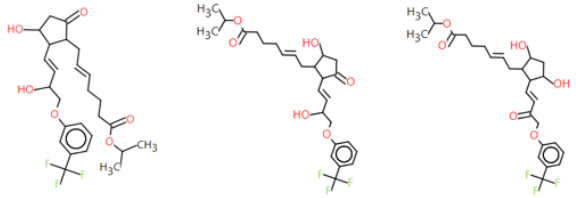
Cloprostenol

Oxidation Products

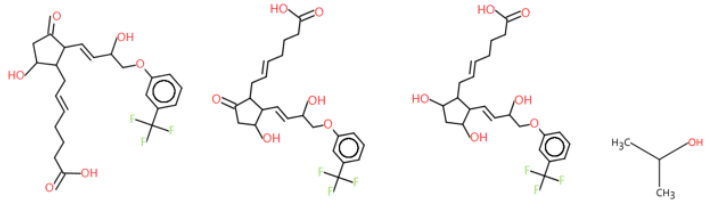


Travoprost

Oxidation Products



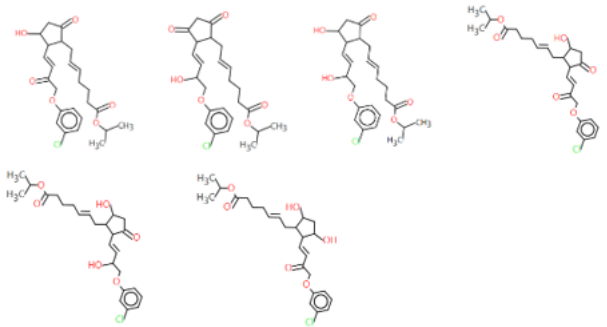
Hydrolysis Products (with or without additional oxidation)



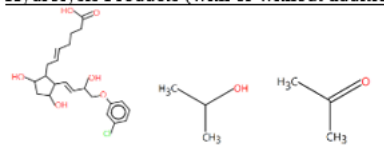
Predicted Hepatic Metabolites (Rat, S9) – OECD QSAR Toolbox

IC

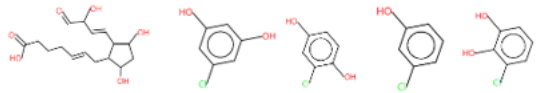
Oxidation Products



Hydrolysis Products (with or without additional oxidation)

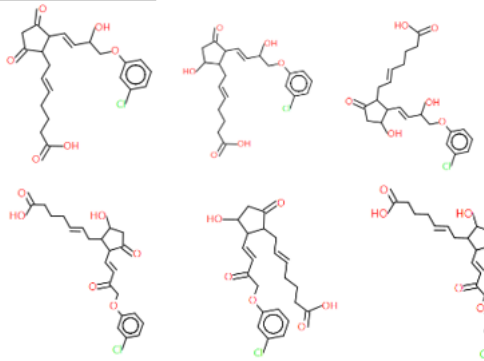


Ether Cleavage Products



Cloprostenol

Oxidation Products



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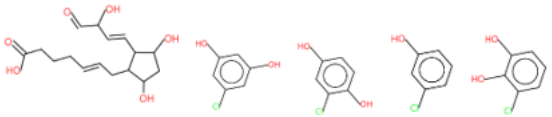
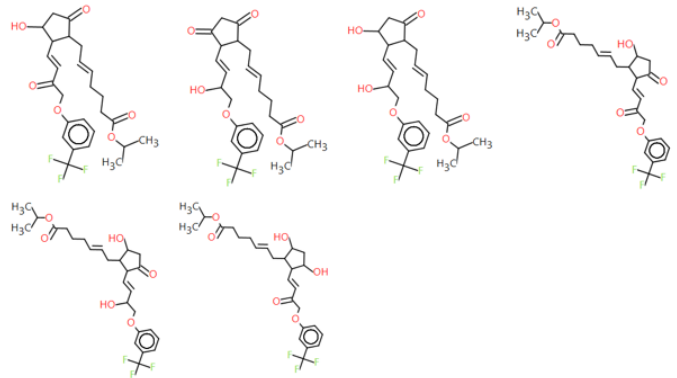
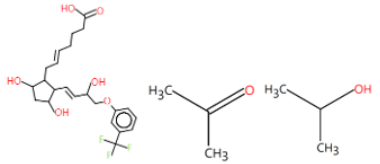


Travoprost

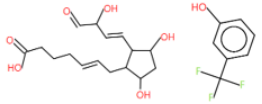
Oxidation Products



Hydrolysis Products (with or without additional oxidation)

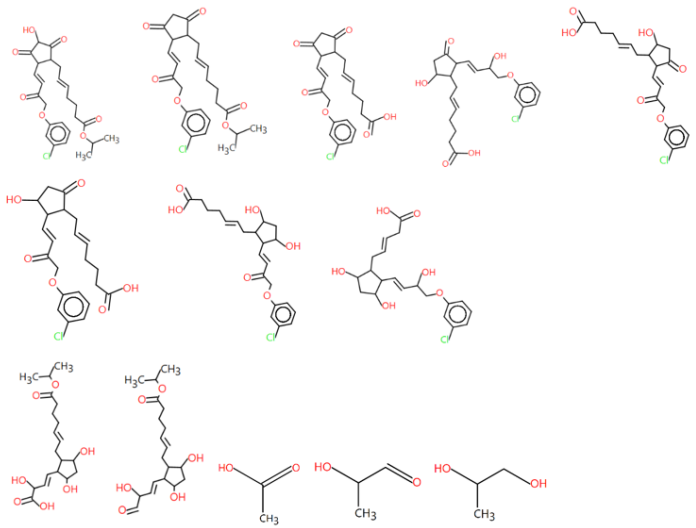


Ether Cleavage Products

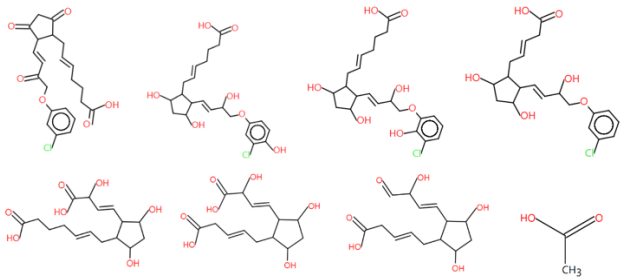


Additional *in vivo* Rat Metabolites – OECD QSAR Toolbox

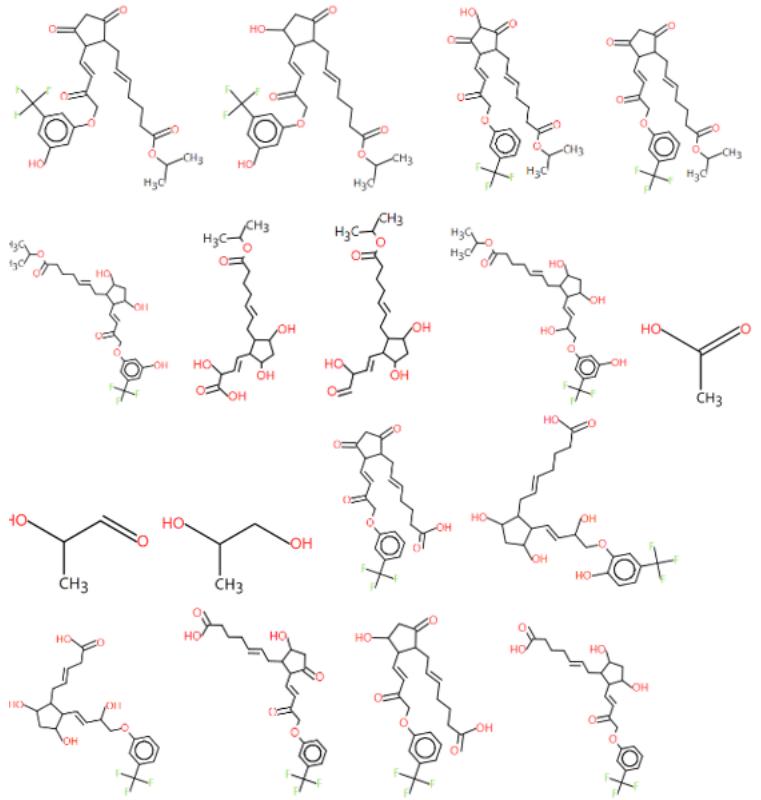
IC



Cloprostenol

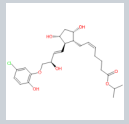
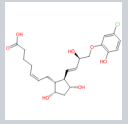
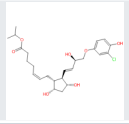
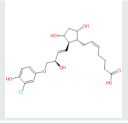
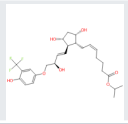
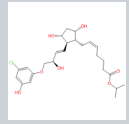
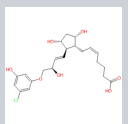
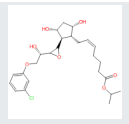
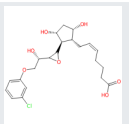
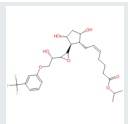
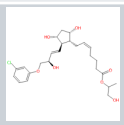
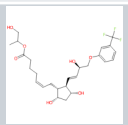
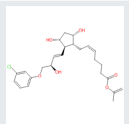
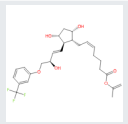
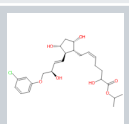
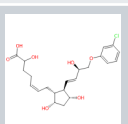
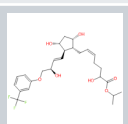
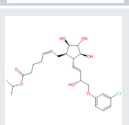
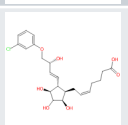
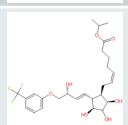
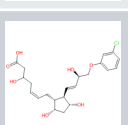


Travoprost

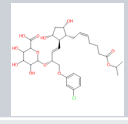
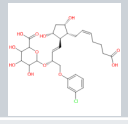
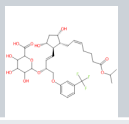
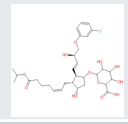
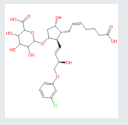
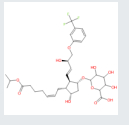
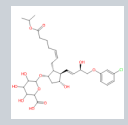
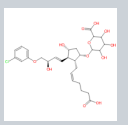
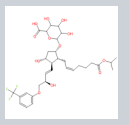
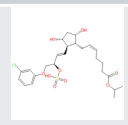
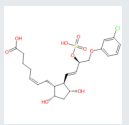
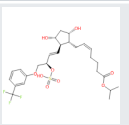
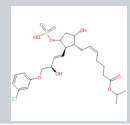
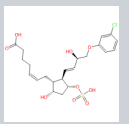
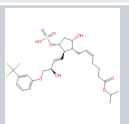
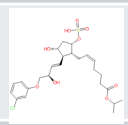
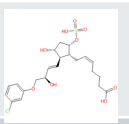
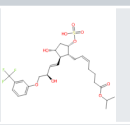
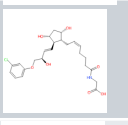


BioTransformer 3.0

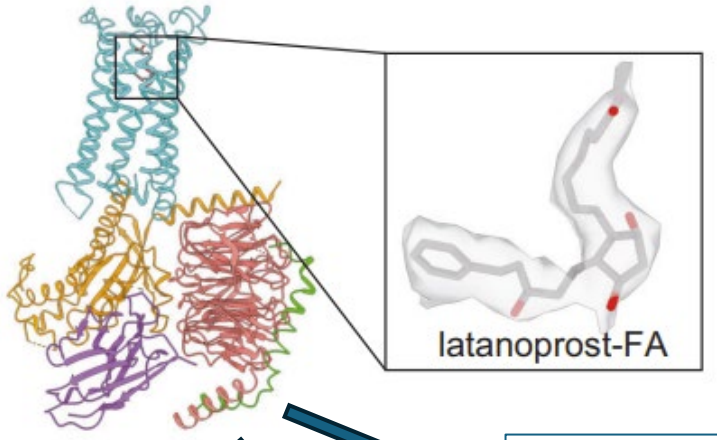
BioTransformer Phase I Predictions

Reaction	Substance: Isopropyl Cloprostenate	Cloprostenol	Travoprost
Hydroxylation para to halide			Not identified
Hydroxylation ortho to halide			
Hydroxylation meta to halide			Not identified
Epoxidation			
Hydroxylation of terminal methyl		N/A	
Terminal desaturation		N/A	
Alpha hydroxylation of carbonyl			
Hydroxylation of alicyclic secondary carbon			
Hydroxylation of acyclic aliphatic secondary carbonyl	Not identified		Not identified

BioTransformer Phase II Predictions

Reaction	Substance: Isopropyl Cloprostenate	Cloprostenol	Travoprost
Alkyl-OH-glucuronidation			
			
			
OH-sulfation			
			
			
Glycine conjugation	Not identified		Not identified
O-glucuronidation of aliphatic acid	Not identified		Not identified
Carnitine conjugation	Not identified		Not identified
Ligation with long-chain fatty acyl-CoA	Not identified		Not identified

Mechanism of Action



Iris color change
FP receptor activation → increased tyrosinase activity (not mediated via cAMP) → increased melanin production in melanosome organelles in iridial melanocytes

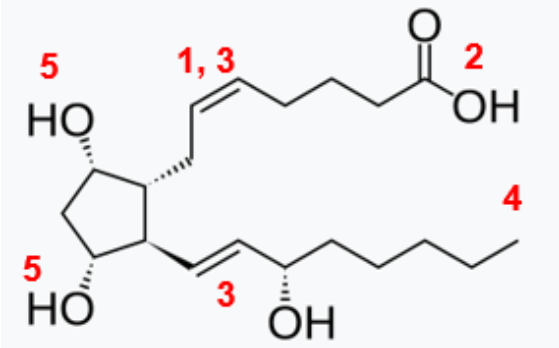
IOP reduction
FP receptor activation → PLC activation → IP3 production → calcium mobilization + cAMP activation

Periorbital fat loss
FP receptor activation → MAPK activation → PPARγ inhibition → inhibition of adipocyte differentiation

Luteolysis, premature parturition, menstruation
FP receptor activation → calcium mobilization → myometrial contraction + vasoconstriction

Cell growth, tumor progression
FP receptor activation → calcium mobilization + calcineurin activation → activation of NFAT transcription factor → increased IL-11 expression

Structural Determinants of FP Receptor Binding

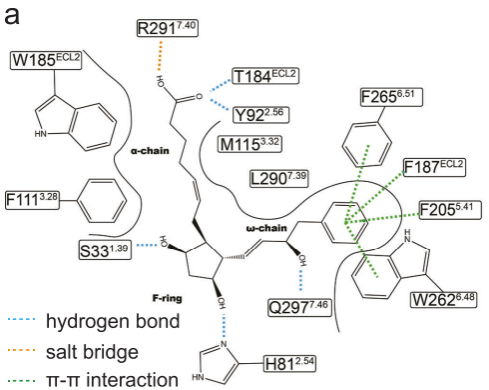


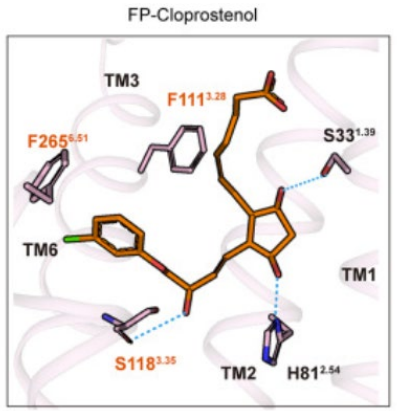
PGF2α

An ideal FP ligand would have the following characteristics:

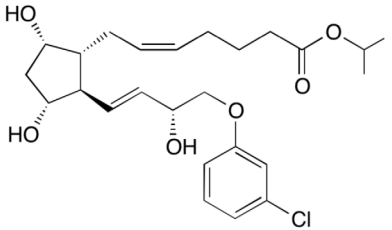
1. Trans conformation on the alpha chain
2. Terminal carboxylic acid on the alpha chain (excludes bimatoprost)
3. Double bonds at the 5,6 (alpha) and 13,14 (omega) positions (excludes latanoprost)
4. Terminal halide-substituted phenoxy moiety (excludes latanoprost and bimatoprost)
5. Two ring hydroxy groups

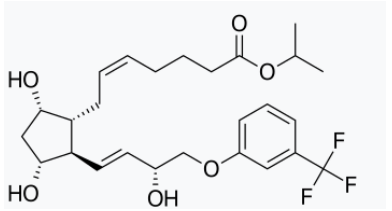
The two ring hydroxy groups, the alpha chain carboxyl group, the alpha chain double bond, and the hydroxy group and benzene ring on the omega chain interact with specific residues on the FP receptor.



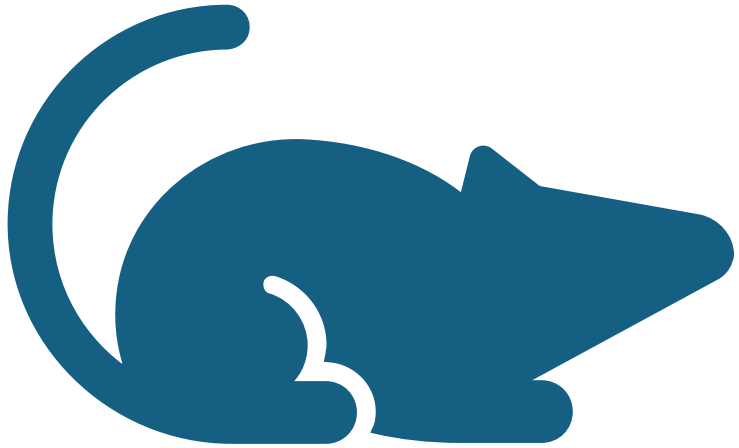


IC (left) and travoprost (right) possess each of the 5 structural features characteristic of an ideal FP ligand.





Receptor Binding and Bioactivity



Prostaglandin Analogue FP Receptor Activation		
Analogue	FP Receptor EC_{50} (free acid)	FP Receptor EC_{50} (prodrug/unhydrolyzed)
Cloprostenol	1.0 nM	In progress
Latanoprost	54.6 nM	126 nM
Travoprost	3.2 nM	42.3 nM
Bimatoprost	5.8 nM	694 nM

Prostaglandin Analogue In Vivo Bioactivity			
Compound	ROI_{15} (µg)	CPD, ED_5 (µg)	Monkey IOP, % change (dose in µg)
Isopropyl cloprostenate	0.3	0.013	-39% (1)
Latanoprost	1.8	0.13	-27% (3)
Travoprost	3	0.015	-29% (0.3)

What about non-FP mechanisms?

Performed predictive modeling using 3 programs

Danish QSAR Models →

Danish QSAR Models Predictions		
Model	**Prediction for IC**	**Prediction for Travoprost**
ER alpha binding (human)	Negative	Out of domain
ER alpha activation (human)	Negative	Out of domain
ER activation (CERAPP data)	Negative	Out of domain
ER beta activation (< 20 uM)	**Negative**	**Negative**
ER beta inhibition (< 10 uM)	**Positive**	**Positive**
ER beta inhibition (< 50 uM)	**Positive**	**Positive**
AR antagonism (human)	**Negative**	**Negative**
AR inhibition (CoMPARA data)	Negative	Out of domain
Aromatase inhibition (< 10 uM)	**Positive**	**Positive**
Aromatase inhibition (< 50 uM)	**Positive**	**Positive**
Retinoic acid receptor inhibition (< 10 uM)	**Negative**	**Negative**
Retinoic acid receptor inhibition (any concentration)	Out of domain	Positive
NIS higher sensitivity	Out of domain	Positive
NIS higher specificity	Out of domain	Positive
Thyroperoxidase inhibition 1	**Negative**	**Negative**
Thyroperoxidase inhibition 2	**Negative**	**Negative**
DIO1 inhibition	**Negative**	**Negative**
DIO2 inhibition	Out of domain	Positive
DIO3 inhibition	**Positive**	**Positive**
TSHR inhibition	Negative	Out of domain
Pregnane X receptor binding (human, in vitro)	**Positive**	**Positive**
Pregnane X receptor activation (human, in vitro)	Positive	Out of domain
AhR agonism, rational sampling (human, in vitro)	**Negative**	**Negative**
AhR agonism, random sampling (human, in vitro)	**Negative**	**Negative**
PPARγ activation (< 20 uM)	**Positive**	**Positive**
PPARγ activation (< 50 uM)	**Positive**	**Positive**
PPARγ inhibition (< 10 uM)	**Positive**	**Positive**
PPARγ inhibition (any concentration)	**Positive**	**Positive**

ER – estrogen receptor; AR – androgen receptor; DIO iodothyronine deiodinase; NIS – sodium iodide symporter; TSHR – thyroid stimulating hormone receptor.

VEGA

VEGA Predictions		
VEGA Model	Prediction for IC	Prediction for Travoprost
CAESAR Developmental toxicity	Toxicant, reliable (ADI = 0.873)	Non-toxicant, not reliable (ADI = 0)
DART Library	Non-toxicant, not reliable (ADI = 0)	Non-toxicant, not reliable (ADI = 0)
ER-mediated effects	**Non-active, reliable (ADI = 0.903)**	**Non-active, reliable (ADI = 0.886)**
ER alpha relative binding affinity	Non-active, reliable (ADI = 0.894)	Active, not reliable (ADI = 0)
AR-mediated effect	Active, not reliable (ADI = 0)	Active, not reliable (ADI = 0)
Thyroid receptor alpha effect	**Non-active, reliable (ADI = 0.953)**	**Non-active, reliable (ADI = 0.946)**
Thyroid receptor beta effect	**Non-active, reliable (ADI = 0.953)**	**Non-active, reliable (ADI = 0.946)**
Glucocorticoid receptor	**Non-active, moderately reliable (ADI = 0.768)**	**Non-active, moderately reliable (ADI = 0.757)**
Thyroperoxidase inhibitory activity	Highly selective inhibitor, not reliable (ADI = 0)	Non-active, moderately reliable (ADI = 0.802)
Steroidogenesis	**Active, reliable (ADI = 0.906)**	**Active, reliable (ADI = 0.89)**
Endocrine disruptor activity screening	No prediction can be made	No prediction can be made
Aromatase activity (IRFMN)	**Non-active, reliable (ADI = 0.956)**	**Non-active, reliable (ADI = 0.935)**
Aromatase activity (TOX21)	Agonist, not reliable (ADI = 0)	Agonist, not reliable (ADI = 0)

OECD QSAR Toolbox

OECD QSAR Toolbox Predictions		
Profilers	Prediction for IC	Prediction for Travoprost
General Mechanistic		
Estrogen Receptor Binding	Strong binder, OH group	Non-binder, MW >500
Hydrolysis half-life (pH 6.5-7.4)	**Very slow**	**Very slow**
Hydrolysis half-life (Ka, pH 7) (Hydrowin)	No value	No value
Estrogen Receptor Binding, with Skin metabolism simulator	**1 x Non binder, non-cyclic structure, 6 x Strong binder, OH group**	**1 x Non binder, non-cyclic structure, 6 x Strong binder, OH group**
Hydrolysis half-life (pH 6.5-7.4), with Skin metabolism simulator	**3 x Very slow, 4 x No value**	**3 x Very slow**
Hydrolysis half-life (Ka, pH 7) (Hydrowin), with Skin metabolism simulator	7 x No value	7 x No value
Estrogen Receptor Binding, with Hydrolysis simulator (neutral)	**1 x Non binder, non-cyclic structure, 1 x Strong binder, OH group**	**1 x Non binder, non-cyclic structure, 1 x Strong binder, OH group**
Hydrolysis half-life (pH 6.5-7.4), with Hydrolysis simulator (neutral)	2 x No value	2 x No value
Hydrolysis half-life (Ka, pH 7) (Hydrowin), with Hydrolysis simulator (neutral)	2 x No value	2 x No value
Endpoint Specific		
Retinoic Acid Receptor Binding	Not possible to classify according to these rules	Not possible to classify according to these rules
DART scheme	**Not known precedent reproductive and developmental toxic potential**	**Not known precedent reproductive and developmental toxic potential**
Retinoic Acid Receptor Binding, with Skin metabolism simulator	7 x Not possible to classify according to these rules	7 x Not possible to classify according to these rules
DART scheme, with Skin metabolism simulator	**7 x Not known precedent reproductive and developmental toxic potential**	**7 x Not known precedent reproductive and developmental toxic potential**
Retinoic Acid Receptor Binding, with Hydrolysis simulator (neutral)	2 x Not possible to classify according to these rules	2 x Not possible to classify according to these rules
DART scheme, with Hydrolysis simulator (neutral)	**2 x Not known precedent reproductive and developmental toxic potential**	**2 x Not known precedent reproductive and developmental toxic potential**

Summary

Read-Across Summary Matrix				
Metric	**Analogue Candidate**			
	Cloprostenol	**Latanoprost**	**Travoprost**	**Bimatoprost**
Structural similarity (Tanimoto score and visual structural comparison)	Highest	Moderate	Highest	Lowest
Physicochemical property similarity (MW, water solubility, and partition coefficient)	Lowest	Moderate	Highest	Moderate
Pharmacokinetic property similarity	Lowest	Moderate	Highest	Lowest
MOA similarity	Highest	Moderate	Highest	Lowest
Bioactivity similarity (hyperemia, IOP reduction)	Not evaluated	Moderate	Highest	Not evaluated
In silico similarity – reproductive, developmental, and other endocrine effects	Not evaluated	Not evaluated	High	Not evaluated

Are the data sufficient to support RAX?

Dose-Response Evaluation of IC Analogues					
Treatment	Study Design	Route of Exposure	NOAEL	LOAEL	Critical Effect
Travoprost	Developmental toxicity study in rats	s.c.	0.1 µg/kg/day	N/A	No evidence of adverse developmental effects.
Travoprost	3-Generation rat study	s.c.	N/A	0.12 µg/kg/day	Reduced litter size
Travoprost	Developmental toxicity study in mice	s.c.	0.3 µg/kg/day	1 µg/kg/day	Increased resorptions
Travoprost	Reproductive toxicity study in rats	s.c.	3 µg/kg/day	10 µg/kg/day	Increased resorptions
Travoprost	Developmental toxicity study in rats	i.v.	3 µg/kg/day	10 µg/kg/day	Increased resorptions
Travoprost	6-Month rat study	s.c.	10 µg/kg/day	100 µg/kg/day	Altered bone histopathology
Travoprost	28-Day toxicity studies in mice and rats	i.v.	1,000 µg/kg/day	N/A	No treatment-related effects on reproductive tissues.
Cloprostenol	1-Month rat study	s.c.	N/A	12.5 µg/kg/day	Ovarian vacuolization
Cloprostenol	3-Generation rat study	oral	15 µg/kg/day	20 µg/kg/day	Reduced neonatal viability
Cloprostenol	3-month rat study	oral	50 µg/kg/day	150 µg/kg/day	Ovarian vacuolization
Cloprostenol	3-Month study in marmosets	oral	50 µg/kg/day	150 µg/kg/day	Myocardial changes; increased testes weights
Cloprostenol or IC	28-Day study in rats and mice	i.p.	N/A	100 µg/kg/day	Degeneration of seminiferous tubules.
Cloprostenol	Developmental toxicity study in rats	oral	100 µg/kg/day	N/A	No evidence of adverse developmental effects.
Cloprostenol	Developmental toxicity study in rabbits	s.c.	0.25 µg/kg/day	N/A	No evidence of adverse developmental effects.

All studies with travoprost were performed in support of an FDA submission and therefore must have met certain quality standards (e.g., GLPs).

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