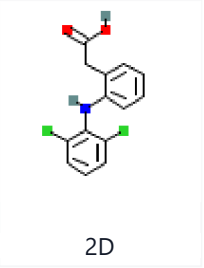
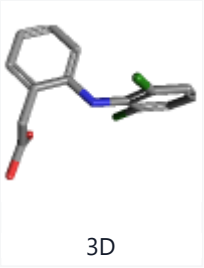
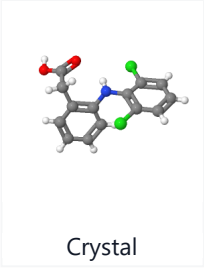
PubChem

COMPOUND SUMMARY

Diclofenac

Cite | Download

PubChem CID	3033
Structure	 2D  3D  Crystal
Chemical Safety	 Acute Toxic Irritant Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula	$C_{14}H_{11}Cl_2NO_2$
Synonyms	diclofenac 15307-86-5 Diclofenac acid dichlofenac Diclophenac View More...
Molecular Weight	296.1 g/mol *Computed by PubChem 2.2 (PubChem release 2021.10.14)*
Dates	Create: 2005-03-25 Modify: 2024-11-16
Description	Diclofenac is a monocarboxylic acid consisting of phenylacetic acid having a (2,6-dichlorophenyl)amino group at the 2-position. It has a role as a non-narcotic analgesic, an antipyretic, an EC 1.14.99.1 (prostaglandin-endoperoxide synthase) inhibitor, a xenobiotic, an environmental contaminant, a drug allergen and a non-steroidal anti-inflammatory drug. It is a secondary amino compound, an amino acid, a dichlorobenzene, an aromatic amine and a monocarboxylic acid. It is functionally related to a

phenylacetic acid and a diphenylamine. It is a conjugate acid of a diclofenac(1-).

▸ ChEBI

Diclofenac is a phenylacetic acid derivative and non-steroidal anti-inflammatory drug (NSAID). NSAIDs inhibit cyclooxygenase (COX)-1 and-2 which are the enzyme responsible for producing prostaglandins (PGs). PGs contribute to inflammation and pain signalling. Diclofenac, like other NSAIDs, is often used as first line therapy for acute and chronic pain and inflammation from a variety of causes. Diclofenac was the product of rational drug design based on the structures of [phenylbutazone], [mefenamic acid], and [indomethacin]. The addition of two chlorine groups in the ortho position of the phenyl ring locks the ring in maximal torsion which appears to be related to increased potency. It is often used in combination with [misoprostol] to prevent NSAID-induced gastric ulcers. Diclofenac was first approved by the FDA in July 1988 under the trade name Voltaren, marketed by Novartis (previously Ciba-Geigy).

▸ DrugBank

Diclofenac is a Nonsteroidal Anti-inflammatory Drug. The mechanism of action of diclofenac is as a Cyclooxygenase Inhibitor. The physiologic effect of diclofenac is by means of Decreased Prostaglandin Production.

▸ FDA Pharm Classes

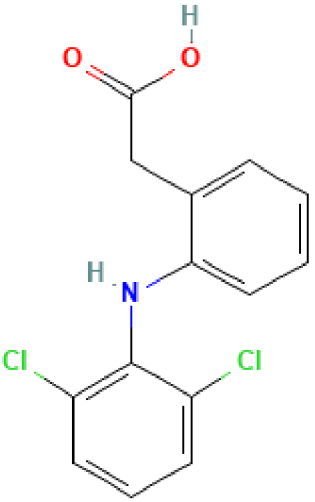
View More...

Contents

1 Structures

1.1 2D Structure

Chemical Structure Depiction



PubChem

1.2 3D Conformer

PubChem

1.3 Crystal Structures

1 of 13	View All
CCDC Number	128771
Associated Article	DOI:10.1107/S0108270197002126
Crystal Structure Data	DOI:10.5517/cc49zx9
Crystal Structure Depiction	

The Cambridge Structural Database

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

2-[2-(2,6-dichloroanilino)phenyl]acetic acid

Computed by Lexichem TK 2.7.0 (PubChem release 2021.10.14)

PubChem

2.1.2 InChI

InChI=1S/C14H11Cl2NO2/c15-10-5-3-6-11(16)14(10)17-12-7-2-1-4-9(12)8-13(18)19/h1-7,17H,8H2,(H,18,19)

Computed by InChI 1.0.6 (PubChem release 2021.10.14)

PubChem

2.1.3 InChIKey

DCOPUUMXTXDBNB-UHFFFAOYSA-N

Computed by InChI 1.0.6 (PubChem release 2021.10.14)

PubChem

2.1.4 SMILES

C1=CC=C(C(=C1)CC(=O)O)NC2=C(C=CC=C2Cl)Cl

Computed by OEChem 2.3.0 (PubChem release 2021.10.14)

PubChem

2.2 Molecular Formula

$C_{14}H_{11}Cl_2NO_2$

Computed by PubChem 2.2 (PubChem release 2021.10.14)

PubChem

2.3 Other Identifiers

2.3.1 CAS

15307-86-5

Australian Industrial Chemicals Introduction Scheme (AICIS); CAS Common Chemistry; ChemIDplus; Drug...

78213-16-8

European Chemicals Agency (ECHA)

2.3.2 Related CAS

15307-81-0 (mono-potassium salt)

- ChemIDplus

2.3.3 European Community (EC) Number

239-348-5

- European Chemicals Agency (ECHA)

616-599-2

- European Chemicals Agency (ECHA)

2.3.4 UNII

144O8QL0L1

- FDA Global Substance Registration System (GSRS)

2.3.5 ChEBI ID

CHEBI:47381

- ChEBI

2.3.6 ChEMBL ID

CHEMBL139

- ChEMBL

2.3.7 DrugBank ID

DB00586

- DrugBank

2.3.8 DSSTox Substance ID

DTXSID6022923

- EPA DSSTox

2.3.9 HMDB ID

HMDB0014724

- Human Metabolome Database (HMDB)

2.3.10 KEGG ID

C01690

- KEGG

D07816

- KEGG

2.3.11 Metabolomics Workbench ID

42917

- Metabolomics Workbench

2.3.12 NCI Thesaurus Code

C28985

- NCI Thesaurus (NCIt)

2.3.13 Nikkaji Number

J8.557J

- Japan Chemical Substance Dictionary (Nikkaji)

2.3.14 PharmGKB ID

PA449293

- PharmGKB

2.3.15 Pharos Ligand ID

MUDSKU2U2VCB

Pharos

2.3.16 RXCUI

3355

NLM RxNorm Terminology

2.3.17 Wikidata

Q244408

Wikidata

2.3.18 Wikipedia

Diclofenac

Wikipedia

2.4 Synonyms

2.4.1 MeSH Entry Terms

Dichlofenal
Diclofenac
Diclofenac Potassium
Diclofenac Sodium
Diclofenac, Sodium
Diclonate P
Diclophenac
Dicrofenac
Feloran
GP 45,840
GP-45,840
GP45,840
Novapirina
Orthofen
Orthophen
Ortofen
Sodium Diclofenac
SR 38
SR-38
SR38
Voltaren
Voltarol

Medical Subject Headings (MeSH)

2.4.2 Depositor-Supplied Synonyms

diclofenac	Voltarol	C

15307-86-5	Diclofenac free acid
Diclofenac acid	Zorovolex
dichlofenac	Zorvolex
Diclophenac	Diclofenamic acid
Diclofenaco	2-(2,6-Dichloroanilino)phenylacetic Acid
Diclofenacum	2-{2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid
2-(2-((2,6-Dichlorophenyl)amino)phenyl)acetic acid	Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-
ProSorb-D	2-[2-(2,6-dichloroanilino)phenyl]acetic acid
Diclofenac resinate	2-((2,6-Dichlorophenyl)amino)benzeneacetic acid

PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	296.1 g/mol	Computed by PubChem 2.2 (PubChem release 2021.10.14)
XLogP3	4.4	Computed by XLogP3 3.0 (PubChem release 2021.10.14)
Hydrogen Bond Donor Count	2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.10.14)
Hydrogen Bond Acceptor Count	3	Computed by Cactvs 3.4.8.18 (PubChem release 2021.10.14)
Rotatable Bond Count	4	Computed by Cactvs 3.4.8.18 (PubChem release 2021.10.14)
Exact Mass	295.0166840 g/mol	Computed by PubChem 2.2 (PubChem release 2021.10.14)
Monoisotopic Mass	295.0166840 g/mol	Computed by PubChem 2.2 (PubChem release 2021.10.14)
Topological Polar Surface Area	49.3Å^2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.10.14)
Heavy Atom Count	19	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	304	Computed by Cactvs 3.4.8.18 (PubChem release 2021.10.14)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem

Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.10.14)

▸ PubChem

3.2 Experimental Properties

3.2.1 Physical Description

Solid

▸ Human Metabolome Database (HMDB)

3.2.2 Color / Form

Crystals from ether-petroleum ether

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 522

▸ Hazardous Substances Data Bank (HSDB)

3.2.3 Melting Point

283-285 °C

▸ DrugBank

156-158 °C

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 522

▸ Hazardous Substances Data Bank (HSDB)

283 - 285 °C

▸ Human Metabolome Database (HMDB)

3.2.4 Solubility

2.37mg/L (at 25 °C)

FINI,A ET AL. (1986)

▸ DrugBank

In water, 2.37 mg/L at 25 °C

Finn A et al; Acta Technol Legis Med 4: 33-44 (1986)

▸ Hazardous Substances Data Bank (HSDB)

4.47e-03 g/L

▸ Human Metabolome Database (HMDB)

3.2.5 LogP

4.51

AVDEEF,A (1997)

▸ DrugBank

log Kow = 4.51

Avdeef A; Seminar on Ionization & Lipophilicity. Log P values measured by pION Inc., Brookline, MA. Avdeef A, Berger C, eds (1987)

▸ Hazardous Substances Data Bank (HSDB)

3.9

▸ Human Metabolome Database (HMDB)

3.2.6 Ionization Efficiency

Ionization mode	Positive
logIE	1.78
pH	2.7
Instrument	Agilent XCT
Ion source	Electrospray ionization
Additive	formic acid (5.3nM)
Organic modifier	MeCN (80%)
Reference	DOI:

Kruve Lab, Ionization & Mass Spectrometry, Stockholm University

3.2.7 Dissociation Constants

Acidic pKa

3.99

*Tested as SID 103191369 in AID 781325: **https://pubchem.ncbi.nlm.nih.gov/bioassay/781325#sid=103191369***

*Comparison of the accuracy of experimental and predicted pKa values of basic and acidic compounds. Pharm Res. 2014; 31(4):1082-95. **DOI:10.1007/s11095-013-1232-z**. **PMID:24249037***

*Tested as SID 103191369 in AID 781326: **https://pubchem.ncbi.nlm.nih.gov/bioassay/781326#sid=103191369***

*Comparison of the accuracy of experimental and predicted pKa values of basic and acidic compounds. Pharm Res. 2014; 31(4):1082-95. **DOI:10.1007/s11095-013-1232-z**. **PMID:24249037***

ChEMBL

Acidic pKa

4.2

*Tested as SID 103191369 in AID 781329: **https://pubchem.ncbi.nlm.nih.gov/bioassay/781329#sid=103191369***

*Comparison of the accuracy of experimental and predicted pKa values of basic and acidic compounds. Pharm Res. 2014; 31(4):1082-95. **DOI:10.1007/s11095-013-1232-z**. **PMID:24249037***

ChEMBL

Acidic pKa

4.3

*Tested as SID 103191369 in AID 781330: **https://pubchem.ncbi.nlm.nih.gov/bioassay/781330#sid=103191369***

*Comparison of the accuracy of experimental and predicted pKa values of basic and acidic compounds. Pharm Res. 2014; 31(4):1082-95. **DOI:10.1007/s11095-013-1232-z**. **PMID:24249037***

ChEMBL

pKa

4.15

SANGSTER (1994)

DrugBank

pKa = 4.15

Sangster J; LOGKOW Databank. Sangster Res. Lab., Montreal Quebec, Canada (1994)

Hazardous Substances Data Bank (HSDB)

3.2.8 Collision Cross Section

157.7 Å^2 $[M+H]^+$ [CCS Type: TW; Method: Major Mix IMS/Tof Calibration Kit (Waters)]

https://www.sciencedirect.com/science/article/pii/S0021967318301894

▸ CCSbase

157.2 Å² [M+H]⁺ [CCS Type: TW]

https://pubs.acs.org/doi/abs/10.1021/acs.analchem.7b00741

▸ CCSbase

151.48 Å² [M+H-H2O]⁺ [CCS Type: TW; Method: calibrated with polyalanine and drug standards]
155.98 Å² [M+H]⁺ [CCS Type: TW; Method: calibrated with polyalanine and drug standards]
166.89 Å² [M+K]⁺ [CCS Type: TW; Method: calibrated with polyalanine and drug standards]

Ross et al. JASMS 2022; 33; 1061-1072. **DOI:10.1021/jasms.2c00111**

▸ CCSbase

156.92 Å² [M+H]⁺
162.87 Å² [M-H]⁻
163.79 Å² [M+Na]⁺

S61 | UJICCSLIB | Collision Cross Section (CCS) Library from UJI | **DOI:10.5281/zenodo.3549476**

▸ NORMAN Suspect List Exchange

3.2.9 Other Experimental Properties

MW 334.24 /Diclofenac potassium salt/

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 522

▸ Hazardous Substances Data Bank (HSDB)

Crystals from water; mp 283-285 °C. UV max (methanol) 283 nm (epsilon 1.01X10+5); (phosphate buffer, pH 7.2) 276 nm (epsilon 1.01X10+5). Solubility at 25 °C (mg/mL): deionized water (pH 5.2) >0; methanol >24; acetone 6; acetonitrile <1; cyclohexane <1; HCl (pH 1.1) <1; phosphate buffer (pH 7.2) 6. pKa 4. Partition coefficient (N-octanol/aqueous buffer): 13.4 /Diclofenac sodium salt/

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 522

▸ Hazardous Substances Data Bank (HSDB)

MW: 411.3; MF: C20H24Cl2N2O3. log Kow = 8 at pH 8.5 /Diclofenac epolamine/

Physicians Desk Reference 65th ed. PDR Network, LLC, Montvale, NJ. 2011, p. 1723

▸ Hazardous Substances Data Bank (HSDB)

3.3 Chemical Classes

3.3.1 Drugs

Pharmaceutical

S120 | DUSTCT2024 | Substances from Second NORMAN Collaborative Dust Trial | ***DOI:10.5281/zenodo.13835254***

- **NORMAN Suspect List Exchange**

3.3.1.1 Human Drugs

Breast Feeding; Lactation; Milk, Human; Analgesic Agents; Anti-inflammatory Agents, Nonsteroidal

- **Drugs and Lactation Database (LactMed)**

Human drug -> Discontinued

- **Drugs@FDA**

Human drug -> None (Tentative Approval); Active ingredient (DICLOFENAC)

- **Drugs@FDA**

Pharmaceuticals

S72 | NTUPHTW | Pharmaceutically Active Substances from National Taiwan University | ***DOI:10.5281/zenodo.3955664***

- **NORMAN Suspect List Exchange**

4 Spectral Information

4.1 1D NMR Spectra

1D NMR Spectra	NMRShiftDB Link

- **NMRShiftDB**

4.1.1 13C NMR Spectra

1 of 2

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Thumbnail	

SpectraBase

2 of 2	
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Thumbnail	

SpectraBase

4.2 Mass Spectrometry

4.2.1 GC-MS

1 of 7	View All
Spectra ID	27820
Instrument Type	EI-B
Ionization Mode	positive

SPLASH	splash10-03xv-3390000000-cd724f772f8ff3648856
Top 5 Peaks	214.0 99.99 216.0 40.27 242.0 39.02 295.0 38.54 215.0 27.73
Thumbnail	
Notes	instrument=JEOL JMS-HX-100

▸ Human Metabolome Database (HMDB)

2 of 7	View All
MoNA ID	JP005136
MS Category	Experimental
MS Type	GC-MS
MS Level	MS1
Instrument	JEOL JMS-HX-100
Instrument Type	EI-B
Ionization Mode	positive
Top 5 Peaks	214 99.99 216 40.27 242 39.02 295 38.54 215 27.73
SPLASH	splash10-03xv-3390000000-cd724f772f8ff3648856

Thumbnail	
License	CC BY-NC-SA

▸ MassBank of North America (MoNA)

4.2.2 MS-MS

1 of 11	View All
Spectra ID	2226990
Ionization Mode	Negative
SPLASH	splash10-0udi-0090000000-659ebbc59b4a39d35b04
Top 5 Peaks	250.0196 100 214.0429 6.48 294.0095 3.01 178.0662 1.42
Thumbnail	

▸ Human Metabolome Database (HMDB)

2 of 11	View All
Spectra ID	2227048
Ionization Mode	Positive
SPLASH	splash10-03xr-0090000000-a3dd8bb749c1165d141e
Top 5 Peaks	214.04355 100 215.0549 98.71 250.02229 14.01 180.07977 2.95 179.07552 1.99
Thumbnail	

▸ Human Metabolome Database (HMDB)

4.2.3 LC-MS

1 of 111	View All
Accession ID	MSBNK-ACES_SU-AS000175
Authors	ACESx, Jonathan W. Martin Group
Instrument	QExactive Orbitrap HF-X (Thermo Scientific)
Instrument Type	LC-ESI-QFT
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	Ramp 20%-70% (nominal)
Fragmentation Mode	HCD

Column Name	Waters; Acquity UPLC BEH C18, 2.1 x 100 mm, 1.7 um, Waters
Retention Time	15.3466
Top 5 Peaks	214.04112 999 214.04071 943 250.01779 457 215.04993 194 278.01395 149
SPLASH	splash10-03di-0090000000-871d7d39f519c50af557
Thumbnail	
License	CC BY

▸ MassBank Europe

2 of 111	View All
Accession ID	MSBNK-ACES_SU-AS000241
Authors	ACESx, Jonathan W. Martin Group
Instrument	QExactive Orbitrap HF-X (Thermo Scientific)
Instrument Type	LC-ESI-QFT
MS Level	MS2
Ionization Mode	NEGATIVE
Ionization	ESI
Collision Energy	Ramp 20%-70% (nominal)
Fragmentation Mode	HCD
Column Name	Waters; Acquity UPLC BEH C18, 2.1 x 100 mm, 1.7 um, Waters
Retention Time	15.3487

Precursor m/z	294.0098
Top 5 Peaks	250.02 999 294.00948 25 178.06718 12 214.04329 11
SPLASH	splash10-0udi-0090000000-75bcd84d59816989a446
Thumbnail	
License	CC BY

▸ MassBank Europe

4.2.4 Other MS

1 of 3	View All
Accession ID	MSBNK-ACES_SU-AS000046
Authors	ACESx, Jonathan W. Martin Group
Instrument	QExactive Orbitrap HF-X (Thermo Scientific)
Instrument Type	LC-APCI-QFT
MS Level	MS2
Ionization Mode	NEGATIVE
Ionization	APCI
Collision Energy	Ramp 20%-70% (nominal)
Fragmentation Mode	HCD
Column Name	Waters; Acquity UPLC BEH C18, 2.1 x 100 mm, 1.7 um, Waters
Retention Time	15.3462

Precursor m/z	294.0096
Top 5 Peaks	250.02022 999 252.01657 396 251.02315 157 221.15451 157 236.10519 129
SPLASH	splash10-0udi-0090000000-d5e88ccb9a3f98f1727d
Thumbnail	
License	CC BY

▸ MassBank Europe

2 of 3	View All
Accession ID	MSBNK-ACES_SU-AS000104
Authors	ACESx, Jonathan W. Martin Group
Instrument	QExactive Orbitrap HF-X (Thermo Scientific)
Instrument Type	LC-APCI-QFT
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	APCI
Collision Energy	Ramp 20%-70% (nominal)
Fragmentation Mode	HCD
Column Name	Waters; Acquity UPLC BEH C18, 2.1 x 100 mm, 1.7 um, Waters
Retention Time	15.3218
Precursor m/z	296.0239

Top 5 Peaks	214.04253 999 250.01901 459 215.05005 180 278.01413 157 296.02386 66
SPLASH	splash10-03di-0090000000-d8e73b9512285d735fbb
Thumbnail	
License	CC BY

▸ MassBank Europe

5 Related Records

5.1 Related Compounds with Annotation

Follow these links to do a live 2D search or do a live 3D search for this compound, sorted by annotation score. This section is deprecated (see here for details), but these live search links provide equivalent functionality to the table that was previously shown here.

▸ PubChem

5.2 Related Compounds

Same Connectivity Count	9
Same Parent, Connectivity Count	129
Same Parent, Exact Count	117
Mixtures, Components, and Neutralized Forms Count	507

Similar Compounds (2D)	View in PubChem Search
Similar Conformers (3D)	View in PubChem Search

PubChem

5.3 Substances

5.3.1 PubChem Reference Collection SID

481107759

PubChem

5.3.2 Related Substances

All Count	1682
Same Count	283
Mixture Count	1399

PubChem

5.3.3 Substances by Category

PubChem

5.4 Entrez Crosslinks

PubMed Count	6044
Protein Structures Count	21
Taxonomy Count	15
OMIM Count	43
Gene Count	1462

▸ PubChem

5.5 Associated Chemicals

Diclofenac sodium; 15307-79-6

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac potassium; 15307-81-0

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac epolamine; 119623-66-4

▸ Hazardous Substances Data Bank (HSDB)

5.6 NCBI LinkOut

▸ NCBI

6 Chemical Vendors

PubChem

7 Drug and Medication Information

7.1 Drug Indication

Diclofenac is indicated for use in the treatment of pain and inflammation from varying sources including inflammatory conditions such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, as well as injury-related inflammation due to surgery and physical trauma. It is often used in combination with [misoprostol] as a gastro-protective agent in patients with high risk of developing NSAID-induced ulcers.

DrugBank

FDA Label

DrugBank

Open Targets

7.2 LiverTox Summary

Diclofenac is a commonly used nonsteroidal antiinflammatory drug (NSAID) used for the therapy of chronic forms of arthritis and mild-to-moderate acute pain. Therapy with diclofenac in full doses is frequently associated with mild serum aminotransferase elevations and, in rare instances, can lead to serious clinically apparent, acute or chronic liver disease.

▸ LiverTox

7.3 Drug Classes

Breast Feeding; Lactation; Milk, Human; Analgesic Agents; Anti-inflammatory Agents, Nonsteroidal

▸ Drugs and Lactation Database (LactMed)

Nonsteroidal Antiinflammatory Drugs

▸ LiverTox

7.4 Drug Transformations

Diclofenac has known transformation products that include 4'-Hydroxydiclofenac and 5-Hydroxydiclofenac.

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | ***DOI:10.5281/zenodo.3754448***

▸ NORMAN Suspect List Exchange

7.5 FDA Medication Guides

1 of 4 View All

Drug	Active Ingredient	Form;Route	Company	Date
Solaraze	Diclofenac Sodium	GEL;TOPICAL	FOUGERA PHARMS	11/14/22

▸ FDA Medication Guides

2 of 4 View All

Drug	Active Ingredient	Form;Route	Company	Date
SOLARAZE	DICLOFENAC SODIUM	GEL;TOPICAL	FOUGERA PHARMS	4/28/21

▸ FDA Medication Guides

3 of 4 View All

Drug	Active Ingredient	Form;Route	Company	Date
VOLTAREN-XR	DICLOFENAC SODIUM	TABLET, EXTENDED RELEASE;ORAL	NOVARTIS	4/28/21

▸ FDA Medication Guides

7.6 FDA Approved Drugs

▸ Drugs@FDA

7.7 FDA Orange Book

▸ FDA Orange Book

7.8 FDA National Drug Code Directory

National Drug Code (NDC) Directory

7.9 Drug Labels

Drug and label

DailyMed

Active ingredient and drug

DailyMed

7.10 Clinical Trials

7.10.1 ClinicalTrials.gov

ClinicalTrials.gov

7.10.2 EU Clinical Trials Register

EU Clinical Trials Register

7.10.3 NIPH Clinical Trials Search of Japan

▸ NIPH Clinical Trials Search of Japan

7.11 Therapeutic Uses

Anti-Inflammatory Agents, Non-Steroidal; Cyclooxygenase Inhibitors

National Library of Medicine's Medical Subject Headings online file (MeSH, 2011)

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac sodium also is used topically as an ophthalmic solution for the treatment of postoperative ocular inflammation in patients undergoing cataract extraction. /Diclofenac sodium; Included in US product labeling/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2108

▸ Hazardous Substances Data Bank (HSDB)

Oral diclofenac sodium has been used for its antipyretic effect in the management of fever, usually associated with infection. In one study, the antipyretic effect of usual dosages of diclofenac sodium as delayed-release (enteric-coated) tablets was about equal to that of usual dosages of aspirin. The drug, however, should not be used routinely as an antipyretic because of its potential adverse effects. /Diclofenac sodium; NOT included in US product labeling/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2108

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac sodium as delayed-release (enteric-coated) tablets also has been used for the symptomatic relief of dysmenorrhea. /Diclofenac sodium; NOT included in US product labeling/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2108

▸ Hazardous Substances Data Bank (HSDB)

For more Therapeutic Uses (Complete) data for DICLOFENAC (22 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

7.12 Drug Warnings

Pregnancy risk category: B /NO EVIDENCE OF RISK IN HUMANS. Adequate, well controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, or, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote but remains a possibility./

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 3567

▸ Hazardous Substances Data Bank (HSDB)

Not recommended for patients with blood dyscrasias (or history of) or bone marrow depression.

Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 390

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac sodium in fixed combination with **misoprostol** is contraindicated in women who are pregnant because **misoprostol** exhibits abortifacient activity and can cause serious fetal harm. In addition, it is recommended that diclofenac in fixed combination with **misoprostol** be used in women of childbearing potential only if they require nonsteroidal anti-inflammatory agent (NSAIA) therapy and are considered at high risk of complications resulting from NSAIA-induced gastric or duodenal ulceration or at high risk of developing gastric or duodenal ulceration. /**Diclofenac sodium**/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2111

▸ Hazardous Substances Data Bank (HSDB)

Caution with **diclofenac sodium**-containing dosage forms in patients who must restrict their **sodium** intake.

Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 390

▸ Hazardous Substances Data Bank (HSDB)

For more Drug Warnings (Complete) data for DICLOFENAC (24 total), please visit the **HSDB record page**.

▸ Hazardous Substances Data Bank (HSDB)

8 Pharmacology and Biochemistry

8.1 Pharmacodynamics

Diclofenac reduces inflammation and by extension reduces nociceptive pain and combats fever. It also increases the risk of developing a gastrointestinal ulcer by inhibiting the production of protective mucus in the stomach.

▸ DrugBank

8.2 MeSH Pharmacological Classification

Anti-Inflammatory Agents, Non-Steroidal

Anti-inflammatory agents that are non-steroidal in nature. In addition to anti-inflammatory actions, they have analgesic, antipyretic, and platelet-inhibitory actions. They act by blocking the synthesis of prostaglandins by inhibiting cyclooxygenase, which converts arachidonic acid to cyclic endoperoxides, precursors of prostaglandins. Inhibition of prostaglandin synthesis accounts for their analgesic, antipyretic, and platelet-inhibitory actions; other mechanisms may contribute to their anti-inflammatory effects. (See all compounds classified as Anti-Inflammatory Agents, Non-Steroidal.)

▸ Medical Subject Headings (MeSH)

Cyclooxygenase Inhibitors

Compounds or agents that combine with cyclooxygenase (PROSTAGLANDIN-ENDOPEROXIDE SYNTHASES) and thereby prevent its substrate-enzyme combination with arachidonic acid and the formation of eicosanoids, prostaglandins, and thromboxanes. (See all compounds classified as Cyclooxygenase Inhibitors.)

▸ Medical Subject Headings (MeSH)

8.3 FDA Pharmacological Classification

1 of 2	
FDA UNII	144O8QL0L1
Active Moiety	DICLOFENAC
Pharmacological Classes	Mechanisms of Action [MoA] - Cyclooxygenase Inhibitors
Pharmacological Classes	Physiologic Effects [PE] - Decreased Prostaglandin Production
Pharmacological Classes	Chemical Structure [CS] - Anti-Inflammatory Agents, Non-Steroidal
Pharmacological Classes	Established Pharmacologic Class [EPC] - Nonsteroidal Anti-inflammatory Drug
FDA Pharmacology Summary	Diclofenac is a Nonsteroidal Anti-inflammatory Drug. The mechanism of action of diclofenac is as a Cyclooxygenase Inhibitor. The physiologic effect of diclofenac is by means of Decreased Prostaglandin Production.

▸ FDA Pharm Classes

2 of 2	
Non-Proprietary Name	DICLOFENAC

Pharmacological Classes	Nonsteroidal Anti-inflammatory Drug [EPC]; Cyclooxygenase Inhibitors [MoA]; Anti-Inflammatory Agents, Non-Steroidal [CS]; Decreased Prostaglandin Production [PE]

▸ National Drug Code (NDC) Directory

8.4 ATC Code

M01AB05

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | ***DOI:10.5281/zenodo.3754448***

S76 | LUXPHARMA | Pharmaceuticals Marketed in Luxembourg | Pharmaceuticals marketed in Luxembourg, as published by d'Gesondheetskeess (CNS, la caisse nationale de sante, www.cns.lu), mapped by name to structures using CompTox by R. Singh et al. (in prep.). List downloaded from ***https://cns.public.lu/en/legislations/textes-coordonnes/liste-med-comm.html****. Dataset* ***DOI:10.5281/zenodo.4587355***

▸ NORMAN Suspect List Exchange

D - Dermatologicals
D11 - Other dermatological preparations
D11A - Other dermatological preparations
D11AX - Other dermatologicals
D11AX18 - Diclofenac

▸ WHO Anatomical Therapeutic Chemical (ATC) Classification

M - Musculo-skeletal system
M02 - Topical products for joint and muscular pain
M02A - Topical products for joint and muscular pain
M02AA - Antiinflammatory preparations, non-steroids for topical use
M02AA15 - Diclofenac

▸ WHO Anatomical Therapeutic Chemical (ATC) Classification

S - Sensory organs
S01 - Ophthalmologicals
S01B - Antiinflammatory agents
S01BC - Antiinflammatory agents, non-steroids
S01BC03 - Diclofenac

▸ WHO Anatomical Therapeutic Chemical (ATC) Classification

M - Musculo-skeletal system
M01 - Antiinflammatory and antirheumatic products
M01A - Antiinflammatory and antirheumatic products, non-steroids
M01AB - Acetic acid derivatives and related substances
M01AB05 - Diclofenac

▸ WHO Anatomical Therapeutic Chemical (ATC) Classification

8.5 Absorption, Distribution and Excretion

Absorption

Diclofenac is completely absorbed from the GI tract but likely undergoes significant first pass metabolism with only 60% of the drug reaching systemic circulation unchanged. Many topical formulations are absorbed percutaneous and produce clinically significant plasma concentrations. Absorption is dose proportional over the range of 25-150 mg. Tmax varies between formulations with the oral solution reaching peak plasma concentrations in 10-40min, the enteric coated tablet in 1.5-2h, and the sustained- and extended-release formulations prolonging Tmax even further. Administration with food has no significant effects on AUC but does delay Tmax to 2.5-12h.

▸ DrugBank

Route of Elimination

Diclofenac is mainly eliminated via metabolism. Of the total dose, 60-70% is eliminated in the urine and 30% is eliminated in the feces. No significant enterohepatic recycling occurs.

▸ DrugBank

Volume of Distribution

Diclofenac has a total volume of distribution of 5-10 L or 0.1-0.2 L/kg. The volume of the central compartment is 0.04 L/kg. Diclofenac distributes to the synovial fluid reaching peak concentration 2-4h after administration. There is limited crossing of the blood brain barrier and cerebrospinal fluid concentrations only reach 8.22% of plasma concentrations. Doses of 50 mg delivered via intramuscular injection produced no detectable diclofenac concentrations in breast milk, however metabolite concentrations were not investigated. Diclofenac has been shown to cross the placenta in mice and rats but human data is unavailable.

▸ DrugBank

Clearance

Diclofenac has a plasma clearance 16 L/h.

▸ DrugBank

Onset of absorption is delayed when **diclofenac sodium** is administered orally as delayed-release (enteric-coated) tablets, but the extent of absorption does not appear to be affected. /**Diclofenac sodium**/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2113

▸ Hazardous Substances Data Bank (HSDB)

Measurable plasma concentrations of diclofenac have been observed in some fasting individuals within 10 minutes of receiving **diclofenac potassium** conventional tablets. /**Diclofenac potassium**/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2113

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac sodium and diclofenac potassium are almost completely absorbed from the GI tract; however, the drugs undergo extensive first-pass metabolism in the liver, with only about 50-60% of a dose of diclofenac sodium or diclofenac potassium reaching systemic circulation as unchanged drug. Diclofenac also is absorbed into systemic circulation following rectal administration and percutaneously following topical application to the skin as a gel or transdermal system.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2113

▸ Hazardous Substances Data Bank (HSDB)

Food decreases the rate of absorption of conventional tablets of diclofenac potassium and of delayed-release (enteric-coated) tablets of diclofenac sodium, resulting in delayed and decreased peak plasma concentrations; however, the extent of absorption is not affected substantially. When diclofenac potassium conventional tablets are administered with food, time to achieve peak plasma concentrations of the drug is increased and peak plasma concentrations of the drug are decreased by approximately 30%. When single doses of diclofenac sodium delayed-release (enteric-coated) tablets are taken with food, the onset of absorption usually is delayed by 1-4.5 hours but may be delayed up to 12 hours in some patients. These food-induced alterations in GI absorption of the drug result from delayed transit of the delayed-release (enteric-coated) tablets to the small intestine, the site of dissolution. When diclofenac sodium extended-release tablets are taken with food, onset of absorption is delayed 1-2 hours and peak plasma concentrations are increased two-fold; however, extent of absorption is not substantially affected. Absorption of diclofenac does not appear to be affected substantially by the presence of food following continuous dosing of the drug. Antacids also may decrease the rate but not the extent of absorption of diclofenac.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2113

▸ Hazardous Substances Data Bank (HSDB)

For more Absorption, Distribution and Excretion (Complete) data for DICLOFENAC (11 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

8.6 Metabolism / Metabolites

Diclofenac undergoes oxidative metabolism to hydroxy metabolites as well as conjugation to glucuronic acid, sulfate, and taurine. The primary metabolite is 4'-hydroxy diclofenac which is generated by CYP2C9. This metabolite is very weakly active with one thirtieth the activity of diclofenac. Other metabolites include 3'-hydroxy diclofenac, 3'-hydroxy-4'methoxy diclofenac, 4',5-dihydroxy diclofenac, an acylglucuronide conjugate, and other conjugate metabolites.

▸ DrugBank

The extent of metabolism of diclofenac sodium in excised viable human skin was investigated using combination HPLC and radioactivity assay. In an earlier diffusion experiment using an in vitro flow-

through diffusion system, radiolabelled **diclofenac sodium** in either lotion (**Pennsaid**) or aqueous solution was applied to viable human skin, either as single dose or multiple dose (8 times over 2 days). In this study, the receptor fluid samples from the diffusion experiment were subjected to extraction and the aliquot was analysed using HPLC to separate diclofenac and authentic metabolites. Based on the radioactivity of each HPLC fraction, the collection time of the fractions was compared with the retention time of diclofenac and metabolites in standard solutions. The samples from a single or multiple dose application of lotion showed radioactivity in mainly one fraction, whose retention time corresponded with diclofenac. Other HPLC fractions showed none or only small amounts of radioactivity within the error range of the assay. The same results were obtained with the pooled samples from the application of the lotion or of aqueous solution. The results suggest that **diclofenac sodium** does not undergo metabolism in viable human epidermis during percutaneous absorption in vitro. Hence, with topical application to human skin in vivo, diclofenac will be delivered with minimal, if any, metabolism. /**Diclofenac sodium**/

PMID:10892898

Tanojo H et al; Eur J Drug Metab Pharmacokinet 24 (4): 345-51 (1999)

▸ **Hazardous Substances Data Bank (HSDB)**

In humans, metabolism of the commonly used nonsteroidal antiinflammatory drug diclofenac /compound/ 1 yields principally the 4'-hydroxy /compound/ 2, 5-hydroxy /compound/ 3, and acyl glucuronide /compound/ 4 metabolites. All three metabolites have been implicated in rare idiosyncratic adverse reactions associated with this widely used drug. Therefore, for mechanistic toxicological studies of /compound/ 1, substantial quantities of 2-4 are required and their syntheses and characterization are described here. Key steps were a convenient two-step preparation of **aniline** /compound/ 5 from **phenol**, efficient and selective 6-iodination of amide /compound/ 18, and high-yielding Ullmann couplings to generate diarylamines /compound/ 11 and /compound/ 21. The acyl glucuronide /compound/ 4 was obtained by Mitsunobu reaction of /compound/ 1 (free acid) with **allyl glucuronate** /compound/ 23 followed by Pd(0) deprotection, using a modification of a published procedure. /Investigators/ report full characterization of /compound/ 4 ... /Investigators/ report also the metabolic fates of the synthetic metabolites: /compound/ 2 and /compound/ 3 were glucuronidated in rats, but only /compound/ 3 formed **glutathione** adducts in vivo and by enzymatic synthesis via a quinoneimine intermediate. A previously undescribed **glutathione** adduct of /compound/ 3 was obtained by enzymatic synthesis. Compound /compound/ 4 formed an imine-linked protein conjugate as evinced by **sodium cyanoborohydride** trapping.

Kenny JR et al; J Med Chem 47 (11): 2816-25 (2004)

▸ **Hazardous Substances Data Bank (HSDB)**

Diclofenac is eliminated predominantly (approximately 50%) as its 4'-hydroxylated metabolite in humans, whereas the acyl glucuronide (AG) pathway appears more important in rats (approximately 50%) and dogs (>80-90%). However, previous studies of diclofenac oxidative metabolism in human liver microsomes (HLMs) have yielded pronounced underprediction of human in vivo clearance. We determined the relative quantitative importance of 4'-hydroxy and AG pathways of diclofenac metabolism in rat, dog, and human liver microsomes. Microsomal intrinsic clearance values (CL(int) = V(max)/K(m)) were determined and used to extrapolate the in vivo blood clearance of diclofenac in these species. Clearance of diclofenac was accurately predicted from microsomal data only when both the AG and the 4'-hydroxy pathways were considered. However, the fact that the AG pathway in HLMs

accounted for ~75% of the estimated hepatic CL(int) of diclofenac is apparently inconsistent with the 4'-hydroxy diclofenac excretion data in humans. Interestingly, upon incubation with HLMs, significant oxidative metabolism of diclofenac AG, directly to 4'-hydroxy diclofenac AG, was observed. The estimated hepatic CL(int) of this pathway suggested that a significant fraction of the intrahepatically formed diclofenac AG may be converted to its 4'-hydroxy derivative in vivo. Further experiments indicated that this novel oxidative reaction was catalyzed by CYP2C8, as opposed to CYP2C9-catalyzed 4'-hydroxylation of diclofenac. These findings may have general implications in the use of total (free + conjugated) oxidative metabolite excretion for determining primary routes of drug clearance and may question the utility of diclofenac as a probe for phenotyping human CYP2C9 activity in vivo via measurement of its pharmacokinetics and total 4'-hydroxy diclofenac urinary excretion.

PMID:12438516

Kumar S et al; J Pharmacol Exp Ther 303 (3): 969-78 (2002)

▸ Hazardous Substances Data Bank (HSDB)

The metabolism of (14)C-diclofenac in mice was investigated following a single oral dose of 10 mg/kg. The majority of the drug-related material was excreted in the urine within 24 hr of administration (49.7%). Liquid chromatographic analysis of urine and fecal extracts revealed extensive metabolism to at least 37 components, with little unchanged diclofenac excreted. Metabolites were identified using a hybrid linear ion-trap mass spectrometer via exact mass determinations of molecular ions and subsequent multi-stage fragmentation. The major routes of metabolism identified included: 1) conjugation with taurine; and 2) hydroxylation (probably at the 4'-and 5-arene positions) followed by conjugation to taurine, glucuronic acid or glucose. Ether, rather than acyl glucuronidation, predominated. There was no evidence for p-benzoquinone-imine formation (i.e. no glutathione or mercapturic acid conjugates were detected). A myriad of novel minor drug-related metabolites were also detected, including ribose, glucose, sulfate and glucuronide ether-linked conjugates of hydroxylated diclofenac derivatives. Combinations of these hydroxylated derivatives with acyl conjugates (glucose, glucuronide and taurine) or N-linked sulfation or glucosidation were also observed. Acyl- or amide-linked-conjugates of benzoic acid metabolites and several indolinone derivatives with further hydroxylated and conjugated moieties were also evident. The mechanisms involved in the generation of benzoic acid and indolinone products indicate the formation reactive intermediates in vivo that may possibly contribute to hepatotoxicity.

PMID:21955289

Sarda S et al; Xenobiotica 42 (2): 179-94 (2012)

▸ Hazardous Substances Data Bank (HSDB)

For more Metabolism/Metabolites (Complete) data for DICLOFENAC (7 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac has known human metabolites that include 4'-hydroxydiclofenac, (2S,3S,4S,5R)-6-[2-[2-(2,6-Dichloroanilino)phenyl]acetyl]oxy-3,4,5-trihydroxyoxane-2-carboxylic acid, and 5-hydroxydiclofenac.

Diclofenac is a known human metabolite of aceclofenac.

▸ NORMAN Suspect List Exchange

Hepatic. Route of Elimination: Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Half Life: 2 hours

▸ Toxin and Toxin Target Database (T3DB)

8.7 Biological Half-Life

The terminal half-life of diclofenac is approximately 2 h, however the apparent half-life including all metabolites is 25.8-33 h.

▸ DrugBank

Following application of diclofenac epolamine transdermal system, the elimination half-life of diclofenac is approximately 12 hours. /Diclofenac epolamine/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2114

▸ Hazardous Substances Data Bank (HSDB)

Following IV administration of diclofenac sodium in healthy adults, the half-life of diclofenac reportedly averages about 3 minutes in the initial distribution phase, about 16 minutes in the intermediate (redistribution) phase, and about 1-2 hours in the terminal (elimination) phase. /Diclofenac sodium/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2114

▸ Hazardous Substances Data Bank (HSDB)

Elimination: Up to 6 hours

Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 377

▸ Hazardous Substances Data Bank (HSDB)

8.8 Mechanism of Action

Diclofenac inhibits cyclooxygenase-1 and -2, the enzymes responsible for production of prostaglandin (PG) G_2 which is the precursor to other PGs. These molecules have broad activity in pain and inflammation and the inhibition of their production is the common mechanism linking each effect of diclofenac. PGE_2 is the primary PG involved in modulation of nociception. It mediates peripheral sensitization through a variety of effects. PGE_2 activates the G_q-coupled EP_1 receptor leading to increased activity of the inositol trisphosphate/phospholipase C pathway. Activation of this pathway releases intracellular stores of calcium which directly reduces action potential threshold and activates protein kinase C (PKC) which contributes to several indirect mechanisms. PGE_2 also activates the EP_4

receptor, coupled to G_s, which activates the adenylyl cyclase/protein kinase A (AC/PKA) signaling pathway. PKA and PKC both contribute to the potentiation of transient receptor potential cation channel subfamily V member 1 (TRPV1) potentiation, which increases sensitivity to heat stimuli. They also activate **tetrodotoxin**-resistant **sodium** channels and inhibit inward **potassium** currents. PKA further contributes to the activation of the P2X3 **purine** receptor and sensitization of T-type **calcium** channels. The activation and sensitization of depolarizing ion channels and inhibition of inward **potassium** currents serve to reduce the intensity of stimulus necessary to generate action potentials in nociceptive sensory afferents. **PGE_2** act via EP_3 to increase sensitivity to **bradykinin** and via EP_2 to further increase heat sensitivity. Central sensitization occurs in the dorsal horn of the spinal cord and is mediated by the EP_2 receptor which couples to G_s. Pre-synaptically, this receptor increases the release of pro-nociceptive neurotransmitters **glutamate**, CGRP, and **substance P**. Post-synaptically it increases the activity of **AMPA** and **NMDA** receptors and produces inhibition of inhibitory glycinergic neurons. Together these lead to a reduced threshold of activating, allowing low intensity stimuli to generate pain signals. **PGI_2** is known to play a role via its G_s-coupled IP receptor although the magnitude of its contribution varies. It has been proposed to be of greater importance in painful inflammatory conditions such as arthritis. By limiting sensitization, both peripheral and central, via these pathways NSAIDs can effectively reduce inflammatory pain. **PGI_2** and **PGE_2** contribute to acute inflammation via their IP and EP_2 receptors. Similarly to β adrenergic receptors these are G_s-coupled and mediate vasodilation through the AC/PKA pathway. **PGE_2** also contributes by increasing leukocyte adhesion to the endothelium and attracts the cells to the site of injury. **PGD_2** plays a role in the activation of endothelial cell release of cytokines through its DP_1 receptor. **PGI_2** and **PGE_2** modulate T-helper cell activation and differentiation through IP, EP_2, and EP_4 receptors which is believed to be an important activity in the pathology of arthritic conditions. By limiting the production of these PGs at the site of injury, NSAIDs can reduce inflammation. **PGE_2** can cross the blood-brain barrier and act on excitatory G_q EP_3 receptors on thermoregulatory neurons in the hypothalamus. This activation triggers an increase in heat-generation and a reduction in heat-loss to produce a fever. NSAIDs prevent the generation of **PGE_2** thereby reducing the activity of these neurons.

▸ **DrugBank**

Diclofenac has pharmacologic actions similar to those of other prototypical NSAIAs. The drug exhibits anti-inflammatory, analgesic, and antipyretic activity. The exact mechanisms have not been clearly established, but many of the actions appear to be associated principally with the inhibition of prostaglandin synthesis. Diclofenac inhibits the synthesis of prostaglandins in body tissues by inhibiting cyclooxygenase; at least 2 isoenzymes, cyclooxygenase-1 (COX-1) and -2 (COX-2) (also referred to as prostaglandin G/H synthase-1 (PGHS-10 and -2 (PGHS-2), respectively), have been identified that catalyze the formation of prostaglandins in the **arachidonic acid** pathway. Diclofenac, like other prototypical NSAIAs, inhibits both COS-1 and COS-2. Although the exact mechanisms have not been clearly established, NSAIAs appear to exert anti-inflammatory, analgesic, and antipyretic activity principally through inhibition of the COS-2 isoenzyme; COX-1 inhibition presumably is responsible for the drugs' unwanted effects on GI mucosa and platelet aggregation.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ **Hazardous Substances Data Bank (HSDB)**

As for all non-steroidal anti-inflammatory drugs the pharmacodynamic effects of **diclofenac sodium** are of anti-inflammatory, analgesic and antipyretic character due to the decrease of the prostaglandin

synthesis from arachidonic acid by inhibition of the cyclo-oxygenase activity. It also induces deleterious effects on gastric and intestinal mucosa and an inhibition of platelet aggregation. /Diclofenac sodium/

European Medicines Agency (EMEA), The European Agency for the Evaluation of Medicinal Products, Veterinary Medicines and Inspections, Committee for Veterinary Medicinal Products; Diclofenac, Summary Report, p.1 (2003). Available from, as of October 24, 2011: https://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true

▸ Hazardous Substances Data Bank (HSDB)

8.9 Human Metabolite Information

8.9.1 Cellular Locations

Cytoplasm
Extracellular
Membrane

▸ Human Metabolome Database (HMDB)

8.9.2 Metabolite Pathways

Diclofenac Action Pathway

▸ Human Metabolome Database (HMDB)

8.10 Biochemical Reactions

▸ PubChem

8.11 Transformations

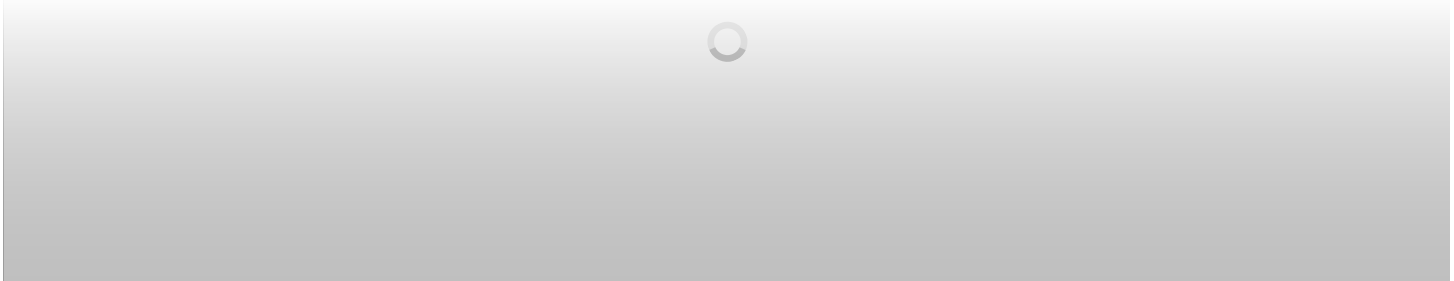
▸ ChEMBL

▸ NORMAN Suspect List Exchange

9 Use and Manufacturing

9.1 Uses

EPA CPDat Chemical and Product Categories



The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products, Scientific Data, volume 5, Article number: 180125 (2018), ***DOI:10.1038/sdata.2018.125***

- **EPA Chemical and Products Database (CPDat)**

MEDICATION

- **Hazardous Substances Data Bank (HSDB)**

For the acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis.

- **Toxin and Toxin Target Database (T3DB)**

9.1.1 Use Classification

Human Drugs -> FDA Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) -> Active Ingredients

- **FDA Orange Book**

Pharmaceuticals

S72 | NTUPHTW | Pharmaceutically Active Substances from National Taiwan University | ***DOI:10.5281/zenodo.3955664***

- **NORMAN Suspect List Exchange**

Pharmaceuticals -> Musculo-skeletal system -> Antiinflammatory and antirheumatic products -> Antiinflammatory and antirheumatic products, non-steroids -> **Acetic acid** derivatives and related substances

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | ***DOI:10.5281/zenodo.3754448***

- **NORMAN Suspect List Exchange**

9.2 Methods of Manufacturing

Oxalyl chloride and **2,6-dichlorodiphenylamine** are condensed to form the N,N-diphenyloxanilyl chloride that cyclizes under Friedel-Crafts conditions to yield 1-(2,6-diphenyl)isatin. Wolff-Kishner reduction of the 3-oxo group gives the lactam, which on hydrolysis affords the free acid. Neutralization with NaOH produces the salt. /**Diclofenac sodium**/

Troy, D.B. (Ed); Remmington The Science and Practice of Pharmacy. 21 st Edition. Lippincott Williams & Williams, Philadelphia, PA 2005, p. 1536

▸ Hazardous Substances Data Bank (HSDB)

Preparation: NL 6604752; A. Sallmann, R. Pfister, US 3558690 (1966, 1971 both to Geigy)

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 522

▸ Hazardous Substances Data Bank (HSDB)

9.3 Formulations / Preparations

Table: Diclofenac Sodium Combination Preparations

Route of Administration	Dosage Form	Strength	Brand or Generic Name (Manufacturer)
Oral	Tablets, delayed-release (enteric-coated core), film-coated	50 mg diclofenac sodium enteric-coated core, with 200 ug of misoprostol outer layer	Arthrotec (Searle)
Oral	Tablets, delayed-release (enteric-coated core), film-coated	75 mg diclofenac sodium enteric-coated core, with 200 ug of misoprostol outer layer	Arthrotec (Searle)

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2114

▸ Hazardous Substances Data Bank (HSDB)

Table: Diclofenac Potassium Preparations

Route of Administration	Dosage Form	Strength	Brand or Generic Name (Manufacturer)
Oral	Tablets	50 mg	Cataflam (Novartis)
Oral	Tablets	50 mg	Diclofenac Potassium Tablets (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2114

▸ Hazardous Substances Data Bank (HSDB)

Table: Diclofenac Epolamine Preparations

Route of Administration	Dosage Form	Strength	Brand or Generic Name (Manufacturer)
Topical	Transdermal System	1.3%	Flector (King)

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2114

▸ Hazardous Substances Data Bank (HSDB)

Table: Diclofenac Sodium Preparations

Route of Administration	Dosage Form	Strength	Brand or Generic Name (Manufacturer)

Oral	Tablets, delayed-release (enteric-coated)	25 mg	Diclofenac Sodium Delayed-release Tablets (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)
Oral	Tablets, delayed-release (enteric-coated)	50 mg	Diclofenac Sodium Delayed-release Tablets (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)
Oral	Tablets, delayed-release (enteric-coated)	75 mg	Diclofenac Sodium Delayed-release Tablets (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)
Oral	Tablets, delayed-release (enteric-coated)	75 mg	Voltaren (Novartis)
Oral	Tablets, extended-release	100 mg	Diclofenac Sodium Extended Release Tablets (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)
Oral	Tablets, extended-release	100 mg	Voltaren-XR (Novartis)
Topical	Gel	1%	Voltaren (Novartis)

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2114

▸ **Hazardous Substances Data Bank (HSDB)**

Table: Diclofenac Preparations

Route of Administration	Dosage Form	Strength	Brand or Generic Name (Manufacturer)
Topical	Gel	3%	Solaraze (Doak)

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 3568

▸ **Hazardous Substances Data Bank (HSDB)**

9.4 General Manufacturing Information

Synthesis: acylation of **N-phenyl-2,6-dichloroaniline** with **chloroacetyl chloride** gives the corresponding **chloroacetanilide**, which is fused with **aluminum chloride** to give **1-(2,6-dichlorophenyl)-2-indolinone**. Hydrolysis of the **indolinone** with dilute aqueous-alcoholic **sodium hydroxide** affords the desired **sodium** salt directly. /**Diclofenac Sodium**/

IATA. Dangerous Goods Regulations. 43rd. Ed. Montreal, Canada and Geneva, Switzerland: International Air Transport Association, Dangerous Goods Regulations, 2002., p. V3 530 (2003)

▸ **Hazardous Substances Data Bank (HSDB)**

Preparation: NL 6604752; A Sallmann, R Pfister, US 3558690 (1966, 1971 both to Geigy)

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 542

▸ Hazardous Substances Data Bank (HSDB)

10 Identification

10.1 Clinical Laboratory Methods

HPLC determination in plasma and urine.

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 522

▸ Hazardous Substances Data Bank (HSDB)

11 Safety and Hazards

11.1 Hazards Identification

11.1.1 GHS Classification

1 of 2 View All

Pictogram(s)	 Acute Toxic Irritant
Signal	Danger
GHS Hazard Statements	H301 (98.4%): Toxic if swallowed [**Danger** Acute toxicity, oral] H311 (85.9%): Toxic in contact with skin [**Danger** Acute toxicity, dermal] H315 (84.4%): Causes skin irritation [**Warning** Skin corrosion/irritation] H319 (84.4%): Causes serious eye irritation [**Warning** Serious eye damage/eye irritation] H335 (84.4%): May cause respiratory irritation [**Warning** Specific target organ toxicity, single exposure; Respiratory tract irritation]
Precautionary Statement Codes	P261, P262, P264, P264+P265, P270, P271, P280, P301+P316, P302+P352, P304+P340, P305+P351+P338, P316, P319, P321, P330, P332+P317, P337+P317, P361+P364, P362+P364, P403+P233, P405, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)

ECHA C&L Notifications Summary	*Aggregated GHS information provided per 64 reports by companies from 12 notifications to the ECHA C&L Inventory. Each notification may be associated with multiple companies.* *Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.*

▸ European Chemicals Agency (ECHA)

11.1.2 Hazard Classes and Categories

Acute Tox. 3 (98.4%)

Acute Tox. 3 (85.9%)

Skin Irrit. 2 (84.4%)

Eye Irrit. 2 (84.4%)

STOT SE 3 (84.4%)

▸ European Chemicals Agency (ECHA)

Acute Tox. 3 (29.5%)

Acute Tox. 4 (40.9%)

Repr. 2 (21.6%)

Repr. 2 (12.5%)

STOT RE 1 (31.8%)

Aquatic Chronic 2 (51.1%)

▸ European Chemicals Agency (ECHA)

11.2 Accidental Release Measures

11.2.1 Disposal Methods

SRP: Expired or waste pharmaceuticals shall carefully take into consideration applicable DEA, EPA, and FDA regulations. It is not appropriate to dispose by flushing the pharmaceutical down the toilet or discarding to trash. If possible return the pharmaceutical to the manufacturer for proper disposal being careful to properly label and securely package the material. Alternatively, the waste pharmaceutical shall be labeled, securely packaged and transported by a state licensed medical waste contractor to dispose by burial in a licensed hazardous or toxic waste landfill or incinerator.

▸ Hazardous Substances Data Bank (HSDB)

SRP: At the time of review, regulatory criteria for small quantity disposal are subject to significant revision, however, household quantities of waste pharmaceuticals may be managed as follows: Mix with wet cat litter or coffee grounds, double bag in plastic, discard in trash.

▸ Hazardous Substances Data Bank (HSDB)

11.3 Handling and Storage

11.3.1 Storage Conditions

Diclofenac sodium 1% gel and **diclofenac epolamine** transdermal system should be stored at 25 °C but may be exposed to temperatures ranging from 15-30 °C. Diclofenac gel should not be frozen.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2114

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac sodium delayed-release (enteric-coated) tablets, **diclofenac sodium** extended-release tablets, and **diclofenac potassium** tablets should be protected from moisture and stored in tight containers at a temperature not exceeding 30 °C. Commercially available **diclofenac sodium** and **misoprostol** tablets should be stored in a dry area at a temperature not exceeding 25 °C.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 214

▸ Hazardous Substances Data Bank (HSDB)

11.4 Regulatory Information

REACH Registered Substance

Status: Active Update: 17-05-2018 **https://echa.europa.eu/registration-dossier/-/registered-dossier/13096**

▸ European Chemicals Agency (ECHA)

11.4.1 FDA Requirements

Indications for use in horses: For the control of pain and inflammation associated with osteoarthritis in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock and pastern) joints. ... Limitations: Do not use in horses intended for human consumption. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

*21 CFR 524.590 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 21, 2011: **https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

The Approved Drug Products with Therapeutic Equivalence Evaluations identifies currently marketed prescription drug products, including **diclofenac sodium**, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act. /**Diclofenac sodium**/

*DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from, as of July 1, 2004: **https://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm***

▸ Hazardous Substances Data Bank (HSDB)

The Approved Drug Products with Therapeutic Equivalence Evaluations identifies currently marketed prescription drug products, including **diclofenac potassium**, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act. /**Diclofenac potassium**/

DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from, as of November 2, 2011: ***https://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm***

▸ Hazardous Substances Data Bank (HSDB)

The Approved Drug Products with Therapeutic Equivalence Evaluations identifies currently marketed prescription drug products, including **diclofenac epolamine**, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act. /**Diclofenac epolamine**/

DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from, as of November 2, 2011: ***https://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm***

▸ Hazardous Substances Data Bank (HSDB)

The Generic Animal Drug and Patent Restoration act requires that each sponsor of an approved animal drug must submit to the FDA certain information regarding patents held for the animal drug or its method of use. The Act requires that this information, as well as a list of all animal drug products approved for safety and effectiveness, be made available to the public. **Diclofenac sodium** is included on this list. /**Diclofenac sodium**/

US FDA/Center for Veterinary Medicine; The Green Book - On Line, Active Ingredients. Diclofenac sodium. Available from, as of November 2, 2011: ***https://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/default.htm***

▸ Hazardous Substances Data Bank (HSDB)

11.5 Other Safety Information

Chemical Assessment

IMAP assessments - **Benzeneacetic acid**, 2-[(2,6-dichlorophenyl)amino]-: Human health tier I assessment

IMAP assessments - **Benzeneacetic acid**, 2-[(2,6-dichlorophenyl)amino]-: Environment tier I assessment

▸ Australian Industrial Chemicals Introduction Scheme (AICIS)

12 Toxicity

12.1 Toxicological Information

12.1.1 Toxicity Summary

The antiinflammatory effects of diclofenac are believed to be due to inhibition of both leukocyte migration and the enzyme cylooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis is responsible for the analgesic effects of diclofenac. Antipyretic effects may be due to action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat dissipation.

▸ Toxin and Toxin Target Database (T3DB)

12.1.2 Hepatotoxicity

Elevated serum aminotransferase levels have been reported in up to 15% of patients taking oral diclofenac chronically, but are greater than 3 times the upper limit of normal in only 2% to 4% (Cases 1 and 2). Clinically apparent and symptomatic liver disease with jaundice due to diclofenac is rare (1 to 5 cases per 100,000 prescriptions, occurring in 1 to 5 persons per 10,000 exposed). Nevertheless, more than a hundred instances of clinically apparent liver injury due to diclofenac have been reported in the literature and, in most case series, diclofenac ranks in the top 10 causes of drug induced liver injury. The time to onset of liver injury varies from within a week to over a year after starting. The majority of cases present within 2 to 6 months (Cases 3 and 4), and the more severe cases tend to present earlier. The pattern of injury is almost exclusively hepatocellular, although cases presenting with mixed patterns have been reported. The clinical picture is that of jaundice preceded by anorexia, nausea, vomiting and malaise. Fever and rash occur in 25% of cases and some cases have immunoallergic features, while others resemble chronic hepatitis and have autoimmune features. In most cases, liver histology reveals an acute lobular hepatitis. However, a cases with prolonged latency diclofenac hepatotoxicity can have clinical and histologic features of chronic hepatitis (Case 2). There seems to be greater susceptibility for diclofenac liver injury among women than men. The injury can be severe, and several cases of acute liver failure have been attributed to diclofenac.

Likelihood score: A (well known cause of clinically apparent liver injury).

Topical forms of diclofenac (solutions, gels, creams, patches) have been associated with only a low rate of serum enzyme elevations (generally less than 1%) that may be no greater than occurs with placebo or vehicle application. However, product labels for topical diclofenac mention the possibility of liver injury and at least one case of clinically apparent liver injury attributed to topical diclofenac has been reported in the literature. Nevertheless, clinically apparent liver injury due to topical forms of diclofenac must be exceedingly rare.

▸ LiverTox

12.1.3 Drug Induced Liver Injury

Compound	diclofenac
DILI Annotation	Most-DILI-Concern

Severity Grade	8
Label Section	Warnings and precautions
References	M Chen, V Vijay, Q Shi, Z Liu, H Fang, W Tong. FDA-Approved Drug Labeling for the Study of Drug-Induced Liver Injury, Drug Discovery Today, 16(15-16):697-703, 2011. PMID:21624500 DOI:10.1016/j.drudis.2011.05.007 M Chen, A Suzuki, S Thakkar, K Yu, C Hu, W Tong. DILIrank: the largest reference drug list ranked by the risk for developing drug-induced liver injury in humans. Drug Discov Today 2016, 21(4): 648-653. PMID:26948801 DOI:10.1016/j.drudis.2016.02.015

▸ Drug Induced Liver Injury Rank (DILIrank) Dataset

12.1.4 Carcinogen Classification

Carcinogen Classification	No indication of carcinogenicity to humans (not listed by IARC).

▸ Toxin and Toxin Target Database (T3DB)

12.1.5 Effects During Pregnancy and Lactation

◉ Summary of Use during Lactation

Data on excretion of diclofenac into milk are poor, but the drug has a short half-life and little glucuronide metabolite formation. Levels in milk appear to be quite low. Most reviewers consider diclofenac to be acceptable during breastfeeding. Other agents having more published information may be preferred, especially while nursing a newborn or preterm infant.

Maternal use of diclofenac topical gel or eye drops would not be expected to cause any adverse effects in breastfed infants. To substantially diminish the amount of drug that reaches the breastmilk after using eye drops, place pressure over the tear duct by the corner of the eye for 1 minute or more, then remove the excess solution with an absorbent tissue.

◉ Effects in Breastfed Infants

In one study, 30 mothers undergoing elective cesarean section were allowed to use 25 mg diclofenac suppositories along with either spinal or spinal and epidural anesthesia with a local anesthetic after delivery. The spinal anesthetic group used an average of 56 mg of diclofenac on the day of delivery and 33 mg on the next day whereas the women receiving both spinal and epidural anesthesia used 21 and 18 mg. No mention was made of adverse effects on the breastfed infants.

A breastfed infant developed urticaria on day 15 of life. Her mother had been taking diclofenac (dosage unspecified) for pain since her cesarean section delivery. Diclofenac is a possible cause of the urticaria; however, the infant had also received hepatitis B vaccination 7 days before and the authors thought that it was a more likely cause of the reaction.

◉ Effects on Lactation and Breastmilk

A randomized, double-blind study was performed in pregnant women scheduled for cesarean section under spinal anesthesia with **bupivacaine** and **fentanyl**. Patients received either 100 mg diclofenac (n = 100), 100 mg **tramadol** (n = 100) or placebo (**glycerin** suppositories) n = 100, all given as rectal suppositories every 8 hours for the first 24 hours after surgery. The time to initiate breastfeeding was

significantly shorter among mothers who received diclofenac than a placebo, 1.5 vs 4.1 hours with breastfeeding support and 3.5 vs 6.2 hours without support. Diclofenac was slightly more effective than tramadol among mothers who received no support (3.5 vs 3.7 hours).

- Drugs and Lactation Database (LactMed)

12.1.6 Exposure Routes

Completely absorbed from the gastrointestinal tract.

- Toxin and Toxin Target Database (T3DB)

12.1.7 Symptoms

Symptoms of overdose include loss of consciousness, increased intracranial pressure, and aspiration pneumonitis.

- Toxin and Toxin Target Database (T3DB)

12.1.8 Acute Effects

- ChemIDplus

12.1.9 Toxicity Data

LD₅₀=390mg/kg (orally in mice)

- Toxin and Toxin Target Database (T3DB)

12.1.10 Interactions

Concomitant use of aspirin and a nonsteroidal anti-inflammatory agent (NSAIA) increases the risk for serious GI events. Because of the potential for increased adverse effects, patients receiving diclofenac should be advised not to take aspirin. There is no consistent evidence that use of low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIAs.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ Hazardous Substances Data Bank (HSDB)

Concurrent use /of alcohol or glucocorticoid corticosteroids or chronic therapeutic use of corticotropin or potassium supplements/ with an nonsteroidal anti-inflammatory drug may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage; however, concurrent use with a glucocorticoid or corticotropin in the treatment of arthritis may provide additional therapeutic benefit and permit reduction of glucocorticoid or corticotropin dosage. /Nonsteroidal anti-inflammatory drugs/

Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 382

▸ Hazardous Substances Data Bank (HSDB)

Nonsteroidal anti-inflammatory drugs may increase the hypoglycemic effect of these medications /oral antidiabetic agents or insulin/ because prostaglandins are directly involved in regulatory mechanisms of glucose metabolism and possibly because of displacement of the oral antidiabetics from serum proteins; dosage adjustments of the antidiabetic agent may be necessary; ... caution with concurrent use is recommended. /Nonsteroidal anti-inflammatory drugs/

Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 382

▸ Hazardous Substances Data Bank (HSDB)

These medications /cefamandole or cefoperazone or cefotetan or plicamycin or valproic acid/ may cause hypoprothrombinemia; in addition, plicamycin or valproic acid may inhibit platelet aggregation; concurrent use with an nonsteroidal anti-inflammatory drug may increase the risk of bleeding because of additive interferences with platelet function and/or the potential occurrence of nonsteroidal anti-inflammatory drug-induced gastrointestinal ulceration or hemorrhage. /Nonsteroidal anti-inflammatory drugs/

Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 383

▸ Hazardous Substances Data Bank (HSDB)

For more Interactions (Complete) data for DICLOFENAC (16 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

12.1.11 Antidote and Emergency Treatment

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask

device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing water. Do not induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160

▸ **Hazardous Substances Data Bank (HSDB)**

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of water for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160

▸ **Hazardous Substances Data Bank (HSDB)**

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag valve mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta agonist such as albuterol for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with diazepam or lorazepam ... . Use proparacaine hydrochloride to assist eye irrigation ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160-1

▸ **Hazardous Substances Data Bank (HSDB)**

Emergency and supportive measures: Maintain on open airway and assist ventilation if necessary. Administer supplemental oxygen. Treat seizures, coma, and hypotension if the occur. Antacids may be used for mild GI upset. Replace fluid losses with intravenous crystalloid solutions. /Nonsteroidal anti-inflammatory drugs/

OLSON, K.R. (Ed). Poisoning and Drug Overdose, Sixth Edition. McGraw-Hill, New York, NY 2012, p. 307

▸ **Hazardous Substances Data Bank (HSDB)**

For more Antidote and Emergency Treatment (Complete) data for DICLOFENAC (7 total), please visit the HSDB record page.

▸ **Hazardous Substances Data Bank (HSDB)**

12.1.12 Human Toxicity Excerpts

/CASE REPORTS/ No signs or symptoms of toxicity were observed in a few patients who ingested 3.75-4 g of diclofenac. However, vomiting and drowsiness occurred in an adolescent who ingested 2.37 g of the drug.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ **Hazardous Substances Data Bank (HSDB)**

/CASE REPORTS/ Acute diclofenac overdosage produces manifestations that are mainly extension of adverse effects of the drug. Loss of consciousness, increased intracranial pressure, and aspiration pneumonitis were reported in a 17 year old male who died 2 days after ingestion 5 g of diclofenac.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ **Hazardous Substances Data Bank (HSDB)**

/CASE REPORTS/ A case of hypoxic brain damage that occurred after intramuscular injection of diclofenac due to a severe anaphylactic reaction /is presented/. A 38-year-old nurse treated herself for acute lower back pain with 100 mg diclofenac intramuscularly. Five minutes later, she collapsed and developed coma and respiratory arrest. After cardiopulmonary resuscitation she was transferred to hospital. On admission she was comatose and received controlled ventilation of the lungs. Magnetic resonance imaging and computerized tomography showed signs of hypoxic brain injury and the patient died from central cardiopulmonary failure 7 days later. Intramuscular treatment with non-steroidal anti-inflammatory drugs such as diclofenac has rare but potentially severe side-effects.

PMID:11580784

Schabitz WR et al; Eur J Anaesthesiol 18 (11): 763-5 (2001)

▸ **Hazardous Substances Data Bank (HSDB)**

/CASE REPORTS/ Upper gastrointestinal tract complications due to non-steroidal anti-inflammatory drugs are well recognised. However, adverse effects on large intestinal mucosa are less common and less well recognised, even though they carry a significant morbidity and mortality. Here we report a case of colonic perforation in a healthy woman without any underlying colonic pathology associated with ingestion of slow release **diclofenac sodium**. /**Diclofenac sodium**/

PMID:10954963

Adhiyaman V et al; Int J Clin Pract 54 (5): 338-9 (2000)

▸ **Hazardous Substances Data Bank (HSDB)**

For more Human Toxicity Excerpts (Complete) data for DICLOFENAC (13 total), please visit the **HSDB record page**.

▸ **Hazardous Substances Data Bank (HSDB)**

12.1.13 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Acute Exposure/ Male ICR mice (CD-1; 25-45 g), fed ad libitum, were administered nephrotoxic doses of diclofenac (DCLF) (100, 200, 300 mg/Kg, po) and sacrificed 24 hr later. Blood was collected to evaluate renal injury (BUN), lipid peroxidation (MDA: **malondialdehyde** levels), and superoxide dismutase (SOD) activity (a marker of oxidative stress). Kidney tissues were analyzed both quantitatively and qualitatively to determine the degree and type of DNA damage, and evaluated histopathologically for the presence of apoptotic characteristics in the nucleus of diverse types of kidney cells. Results show that diclofenac is a powerful nephrotoxicant (at 100, 200, and 300 mg/kg: 4.7-, 4.9-, and 5.0-fold increases in BUN compared to the control, respectively) and a strong inducer of oxidative stress (significant increase in MDA levels). Oxidative stress induced by DCLF was also coupled with massive kidney DNA fragmentation (100, 200, and 300 mg/kg: 3-, 8-, and 10-fold increases compared to control, respectively). A dose-dependent increase in MDA levels and SOD activity was also observed, which indicated a link between oxidative stress and nephrotoxicity. Qualitative analysis of DNA fragmentation by gel electrophoresis showed a DNA ladder indicative of Ca2+-Mg2+-endonuclease activation. Histopathological examination of kidney sections revealed numerous apoptotic nuclei across proximal and distal tubular cell linings. Collectively, these data suggest that DCLF-induced nephrotoxicity may involve production of reactive oxygen species leading to oxidative stress and massive genomic DNA fragmentation, and these two free radical mediated events may ultimately translate into apoptotic cell death of kidney cells in vivo, and reveal a DNA-active role for DCLF.

PMID:11440826

Hickey EJ et al; Free Radic Biol Med 31 (2): 139-52 (2001)

▸ **Hazardous Substances Data Bank (HSDB)**

/LABORATORY ANIMALS: Acute Exposure/ Adult male ICR mice (CD-1 strain) were administered a single intraperitoneal injection of **diclofenac sodium** at 32.5, 65 and 104 mg/kg body weight. Signs of toxicity manifest as hypoactivity were observed in mice of the highest dose group at 24 and 48 hours. No deaths were reported in this study. /**Diclofenac sodium**/

European Medicines Agency (EMEA), The European Agency for the Evaluation of Medicinal Products, Veterinary Medicines and Inspections, Committee for Veterinary Medicinal Products; Diclofenac, Summary Report, p.3 (2003). Available from, as of October 24, 2011: ***https://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true***

▸ **Hazardous Substances Data Bank (HSDB)**

/LABORATORY ANIMALS: Acute Exposure/ Diclofenac tolerance was investigated in cattle and pigs administrated 2.5 mg/kg bw/day for six days. No clinical signs and adverse effects on biochemical parameters, attributable to treatment, were observed in the target species. Adverse effects on hematological parameters (decrease in hematocrit) were observed in cattle, but not in pigs. Histopathology of injected muscle showed polymorphous inflammatory infiltration alone and with necrotic spots in few samples (10 out of 96 cattle and 15 out of 95 pigs) of the injected sites. No drug related changes were observed in kidney and liver, other organs not being investigated. No information on frequency and severity of gastro-intestinal lesions were included in the studies.

European Medicines Agency (EMEA), The European Agency for the Evaluation of Medicinal Products, Veterinary Medicines and Inspections, Committee for Veterinary Medicinal Products; Diclofenac, Summary Report, p.4 (2003). Available from, as of October 24, 2011: ***https://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true***

▸ Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Diclofenac sodium was administered orally (capsules) at 0.3 or 1 mg/kg bw/day to 2 male and 2 female Beagle dogs per group for four weeks. At the lowest dose cortical tubular dilatation was observed in the kidneys of most animals. In addition, females showed urothelial hyperplasia in the renal papillae. The high dosed animals showed severe effects at gastro-intestinal, kidney and spleen sites accompanied by diarrhea, anemia, protein loss and kidney dysfunction. Chronic inflammation of the livers of treated males and females was seen, in females associated with bile duct proliferation. One high dosed male had to be sacrificed in extremis. /Diclofenac sodium/

European Medicines Agency (EMEA), The European Agency for the Evaluation of Medicinal Products, Veterinary Medicines and Inspections, Committee for Veterinary Medicinal Products; Diclofenac, Summary Report, p.3 (2003). Available from, as of October 24, 2011: ***https://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true***

▸ Hazardous Substances Data Bank (HSDB)

For more Non-Human Toxicity Excerpts (Complete) data for DICLOFENAC (19 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

12.1.14 Non-Human Toxicity Values

LD50 Monkey oral 3200 mg/kg /Diclofenac sodium/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ Hazardous Substances Data Bank (HSDB)

LD50 Dog oral 500 mg/kg /Diclofenac sodium/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ Hazardous Substances Data Bank (HSDB)

LD50 Rat oral 55-240 mg/kg /Diclofenac sodium/

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ Hazardous Substances Data Bank (HSDB)

12.1.15 Populations at Special Risk

Many of the spontaneous reports of fatal adverse GI effects in patients receiving nonsteroidal anti-inflammatory agent (NSAIA)s involve geriatric individuals. NSAIAs, including diclofenac, should be used with caution in geriatric patients 65 years of age or older.... Diclofenac is substantially excreted by the kidneys, and the risk of toxicity may be greater in patients with renal impairment. Because geriatric patients are more likely to have decreased renal function, diclofenac should be used with caution; it may be useful to monitor renal function in such patients.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2111

▸ Hazardous Substances Data Bank (HSDB)

Diclofenac should be used with extreme caution and under close supervision in patients with a history of GI bleeding or peptic ulceration, and such patients should receive an appropriate ulcer preventive regimen. All patients considered at increased risk of potentially serious adverse GI effects (e.g., geriatric patients, those receiving high therapeutic dosages of nonsteroidal anti-inflammatory agent (NSAIA)s, those with a history of peptic ulcer disease, those receiving anticoagulants or corticosteroids concomitantly) should be monitored closely for signs and symptoms of ulcer perforation or GI bleeding. To minimize the potential risk of adverse GI effects, the lowest effective dosage and shortest possible duration of therapy should be employed. For patients who are at high risk, therapy other than an NSAIA should be considered.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2110

▸ Hazardous Substances Data Bank (HSDB)

Because of the potential for serious adverse reactions to diclofenac in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

American Society of Health-System Pharmacists 2011; Drug Information 2011. Bethesda, MD. 2011, p. 2112

▸ Hazardous Substances Data Bank (HSDB)

12.1.16 Protein Binding

Diclofenac is over 99.7% bound to serum proteins, primarily albumin. It is undergoes limited binding to lipoproteins as well with 1.1% bound to HDL, 0.3% to LDL, and 0.15% to VLDL.

▸ DrugBank

12.2 Ecological Information

12.2.1 Ecotoxicity Excerpts

/BIRDS and MAMMALS/ The nonsteroidal anti-inflammatory drug diclofenac is extremely toxic to Old World Gyps vultures (median lethal dose ~0.1-0.2 mg/kg), evoking visceral gout, renal necrosis, and mortality within a few days of exposure. Unintentional secondary poisoning of vultures that fed upon carcasses of diclofenac-treated livestock decimated populations in the Indian subcontinent. Because of the widespread use of diclofenac and other cyclooxygenase-2 inhibiting drugs, a toxicological study was undertaken in turkey vultures (Cathartes aura) as an initial step in examining sensitivity of New World scavenging birds. Two trials were conducted entailing oral gavage of diclofenac at doses ranging from 0.08 to 25 mg/kg body weight. Birds were observed for 7 days, blood samples were collected for plasma chemistry (predose and 12, 24, and 48 hr and 7 days postdose), and select individuals were necropsied. Diclofenac failed to evoke overt signs of toxicity, visceral gout, renal necrosis, or elevate plasma **uric acid** at concentrations greater than 100 times the estimated median lethal dose reported for Gyps vultures. For turkey vultures receiving 8 or 25 mg/kg, the plasma half-life

of diclofenac was estimated to be 6 hr, and it was apparently cleared after several days as no residues were detectable in liver or kidney at necropsy. Differential sensitivity among avian species is a hallmark of cyclooxygenase-2 inhibitors, and despite the tolerance of turkey vultures to diclofenac, additional studies in related scavenging species seem warranted.

Rattner BA et al; Environ Toxicol Chem 27 (11): 2341-5 (2008)

▸ **Hazardous Substances Data Bank (HSDB)**

/AQUATIC SPECIES/ One of the most frequently detected pharmaceuticals in environmental **water** samples is the anti-rheumatic drug, diclofenac. Despite its increasing environmental significance, investigations concerning the effects of this drug on the early developmental stages of aquatic species are lacking up to now. To determine the developmental toxicity and proteotoxicity of this drug on the growing fish embryos, eggs of zebrafish were exposed to six concentrations of diclofenac (0, 1, 20, 100, 500, 1000, and 2000 microgl(-1)) using **DMSO** as solvent. Early life stage parameters such as egg and embryo mortality, gastrulation, somite formation, movement and tail detachment, pigmentation, heart beat, and hatching success were noted and described within 48- and 96-h of exposure. After the 96-h exposure, the levels of stress proteins (hsp 70) were determined in both the diclofenac-treated and respective **DMSO** controls. Results showed no significant inhibition in the normal development until the end of 96 h for all exposure groups. However, there was a delay in the hatching time among embryos exposed to 1000 and 2000 microgl(-1). Late-hatched embryos (108 h) did not differ morphologically from normally hatched embryos. The mortality and average heart rate data did not show significant differences for all embryos in both diclofenac-treated and **DMSO** control groups. No significant malformations were likewise noted among all developing embryos throughout the exposure period. The levels of heat shock proteins in diclofenac-treated and control embryos did not differ significantly. **DMSO** control embryos, on the other hand, showed a concentration-dependent increase in hsp 70 levels. We suggest possible modulating effect of diclofenac in **DMSO**-triggered expression of stress proteins and this might have a possible repercussion on the use of **DMSO** as solvent in any toxicity assay. Since the present data indicate no significant embryotoxicity and proteotoxicity induced by diclofenac and due to the fact that the concentrations of diclofenac used in the present study is up to 2000-fold higher than the concentrations detected in the environment, it is unlikely that this drug would pose a hazard to early-life stages of zebrafish.

PMID:15234162

Hallare AV et al; Chemosphere 56 (7): 659-66 (2004)

▸ **Hazardous Substances Data Bank (HSDB)**

/AQUATIC SPECIES/ In the present study, cytopathology was investigated in the liver, kidney, gills and gut of rainbow trout (Oncorhynchus mykiss) exposed to five different concentrations (1, 5, 20, 100 and 500 ug/L) of the anti-inflammatory drug diclofenac under laboratory conditions. The lowest observed effect concentration (LOEC) for cytological alterations in liver, kidney and gills was 1 ug/L. In the gut, however, no diclofenac-induced cytopathology occurred. As the most prominent reactions induced by diclofenac (1) in the kidney, a severe accumulation of protein in the tubular cells (so called hyaline droplet degeneration), macrophage infiltration and structural alterations (dilation, vesiculation) of the endoplasmic reticulum (ER) in the proximal and distal renal tubules were observed. Furthermore, shortening of podocytes and their retraction from the basal lamina, a thickening of the basal lamina, the formation of desmosomes, and necrosis of endothelial cells in the renal corpuscles occurred; (2) in the liver, the most striking reactions were the collapse of the cellular compartmentation as well as the

glycogen depletion of hepatocytes; (3) in the gills, pillar cell necrosis, hypertrophy of chloride cells, and epithelium lifting became evident in the secondary lamellae.

PMID:15145225

Triebskorn R et al; Aquat Toxicol 68 (2): 151-66 (2004)

▸ Hazardous Substances Data Bank (HSDB)

/AQUATIC SPECIES/ ...The impact of diclofenac on river biofilm communities was investigated at exposures of 10 and 100 ug/L of diclofenac or its molar equivalent in carbon and nutrients. Experiments were carried out with river water during spring and summer using rotating annular reactors as model systems. Diclofenac or nutrients at 10 ug/L were observed to have no significant effect on algal, bacterial, and cyanobacterial biomass in spring, whereas in the summer the nutrient equivalent reduced algal biomass and diclofenac reduced cyanobacterial biomass relative to control biofilms ($p<0.05$). In contrast, at 100 ug/L diclofenac or nutrients, the result was increased cyanobacterial and bacterial biomass, respectively, relative to control biofilms in spring. In summer, 100 ug/L diclofenac significantly increased bacterial biomass and the nutrient treatment had no significant effect ($p<0.05$); both treatments resulted in increased biofilm thickness. The glycoconjugate composition of the exopolysaccharide matrix was influenced differentially by the treatments in both seasons. Biolog assessments of carbon use indicated that 100 ug/L diclofenac or nutrients resulted in significant depressions in the use of carbon sources in summer and significant increases in spring. Impacts on protozoan and micrometazoan populations also were assessed. Denaturing gradient gel electrophoresis analyses of community DNA and fluorescent in situ hybridization studies indicated that diclofenac had significant effects on the nature of the bacterial community in comparison with control and nutrient-treated river biofilm communities.

Lawrence JR et al; Environ Toxicol Chem 26 (4): 573-82 (2007)

▸ Hazardous Substances Data Bank (HSDB)

For more Ecotoxicity Excerpts (Complete) data for DICLOFENAC (7 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

12.2.2 Environmental Fate / Exposure Summary

Diclofenac's production and use as an anti-inflammatory may result in its release to the environment through various waste streams. If released to air, an estimated vapor pressure of 6.1X10-8 mm Hg at 25 °C indicates diclofenac will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase diclofenac will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 0.8 hrs. Particulate-phase diclofenac will be removed from the atmosphere by wet and dry deposition. If released to soil, diclofenac is expected to have moderate mobility based upon an estimated Koc of 245. The pKa of diclofenac is 4.15, indicating that this compound will exist almost entirely in the dissociated form in the environment and anions generally do not adsorb more strongly to organic carbon and clay than their neutral counterparts nor do anions volatilize. Volatilization from moist soil is not expected because the compound exists as an anion and anions do not volatilize. Diclofenac is not expected to volatilize from dry soil surfaces based upon the estimated vapor pressure.

Biodegradation in the environment is not an important fate process based upon little or no biodegradation using a freshwater inoculum. If released into water, diclofenac is expected to adsorb to suspended solids and sediment based upon the estimated Koc. A pKa of 4.15 indicates diclofenac will exist almost entirely in the ionized form at pH values of 5 to 9 and therefore volatilization from water surfaces is not expected to be an important fate process. An estimated BCF of 3 suggests the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions. Direct photolysis is the predominant removal process in freshwater, exhibiting a half-life of 8 days. Occupational exposure to diclofenac may occur through dermal contact with this compound at workplaces where diclofenac is produced or used. Monitoring data indicate that the general population may be exposed to diclofenac via ingestion of drinking water, dermal contact with this compound, and pharmaceutical use of consumer products containing diclofenac. (SRC)

▸ Hazardous Substances Data Bank (HSDB)

12.2.3 Artificial Pollution Sources

Diclofenac's production and use as an anti-inflamatory(1) may result in its release to the environment through various waste streams(SRC).

(1) O'Neil MJ, ed; The Merck Index. 14th ed. Whitehouse Station, NJ: Merck and Co., Inc. p. 552 (2006)

▸ Hazardous Substances Data Bank (HSDB)

12.2.4 Environmental Fate

TERRESTRIAL FATE: Based on a classification scheme(1), a Koc value of 245(SRC), from a log Koc of 2.39(2), indicates that diclofenac is expected to have moderate mobility in soil(SRC). The pKa of diclofenac is 4.15(3), indicating that this compound will exist almost entirely in the dissociated form in the environment and anions generally do not adsorb more strongly to organic carbon and clay than their neutral counterparts(4). Volatilization from moist soil is not expected because the compound exists as an anion and anions do not volatilize. Diclofenac is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 6.1X10-8 mm Hg(SRC), determined from a fragment constant method(5). Little or no biodegradation using a freshwater inoculum(6) suggests that biodegradation is not an important environmental fate process in soil(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983)

(2) Barron L et al; Analyst 134: 663-670 (2009)

(3) Sangster J; LOGKOW Databank. Sangster Res. Lab., Montreal Quebec, Canada (1994)

(4) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds. Boca Raton, FL: Lewis Publ (2000)

(5) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)

(6) Buser HR et al; Environ Sci Technol 32: 3449-56 (1998)

▸ Hazardous Substances Data Bank (HSDB)

AQUATIC FATE: Based on a classification scheme(1), a Koc value of 245(SRC), from a log Koc of 2.39(2), indicates that diclofenac is expected to adsorb to suspended solids and sediment(SRC). The pKa is 4.15(3), indicating that diclofenac will exist almost entirely in the anion form at pH values of 5 to 9 and therefore volatilization from **water** surfaces is not expected to be an important fate process. According to a classification scheme(4), an estimated BCF of 3(SRC), from its log Kow of 4.51(5) and a regression-derived equation(6), suggests the potential for bioconcentration in aquatic organisms is low(SRC). Little or no biodegradation using a freshwater inoculum(7) suggests that biodegradation is not an important environmental fate process in **water**. Direct photolysis is the predominant removal process in freshwater, exhibiting a half-life of 8 days(8).

(1) Swann RL et al; Res Rev 85: 17-28 (1983)

(2) Barron L et al; Analyst 134: 663-670 (2009)

(3) Sangster J; LOGKOW Databank. Sangster Res. Lab., Montreal Quebec, Canada (1994)

(4) Franke C et al; Chemosphere 29: 1501-14 (1994)

(5) Avdeef A; Seminar on Ionization & Lipophilicity. Log P values measured by pION Inc., Brookline, MA. Avdeef A, Berger C, eds (1987)

(6) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999)

(7) Buser HR et al; Environ Sci Technol 32: 3449-56 (1998)

(8) Tixier C et al; Environ Sci Technol 37: 1061-68 (2003)

▸ **Hazardous Substances Data Bank (HSDB)**

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), diclofenac, which has an estimated vapor pressure of 6.1X10-8 mm Hg at 25 °C(SRC), determined from a fragment constant method(2), will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase diclofenac is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals(SRC); the half-life for this reaction in air is estimated to be 0.8 hours(SRC), calculated from its rate constant of 1.6X10-10 cu cm/molecule-sec at 25 °C(SRC) that was derived using a structure estimation method(3). Particulate-phase Diclofenac may be removed from the air by wet or dry deposition(SRC).

(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988)

(2) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)

(3) Meylan WM, Howard PH; Chemosphere 26: 2293-99 (1993)

▸ **Hazardous Substances Data Bank (HSDB)**

12.2.5 Environmental Biodegradation

AEROBIC: Diclofenac degradation in a freshwater inoculum from Lake Geifense, Swizterland and incubated for 37 days was found to be negligible(1). At low concentrations (3-35 uM), the compound was biodegraded when incubated in a river sediment consortia from the creek Muenzbach (Freiberg/Saxony), as indicated by the metabolite **p-benzoquinone imine** of **5-hydroxydiclofenac**; concentrations of up to 260uM proved toxic(2). Diclofenac, present at 50 mg/L, reached 1.1% of its theoretical BOD in 75 days using a wastewater inoculum from the Jyvaskyla, Finland sewage treatment plant in the 301F Manometric respirometry test(3).

(1) Buser HR et al; Environ Sci Technol 32: 3449-56 (1998)

(2) Groning J et al; Chemosphere 69: 509-516 (2007)

(3) Lahti M, Oikari A; Arch Environ Contam Toxicol 61: 202-210 (2010)

▸ Hazardous Substances Data Bank (HSDB)

ANAEROBIC: Diclofenac, present at 204 ug/L, exhibited 1-13% cumulative **methane** production in 181 days using a wastewater inoculum from the Jyvaskyla, Finland sewage treatment plant incubated under anaerobic conditions(1).

(1) Lahti M, Oikari A; Arch Environ Contam Toxicol 61: 202-210 (2010)

▸ Hazardous Substances Data Bank (HSDB)

12.2.6 Environmental Abiotic Degradation

The rate constant for the vapor-phase reaction of diclofenac with photochemically-produced hydroxyl radicals has been estimated as 1.6X10-10 cu cm/molecule-sec at 25 °C(SRC) using a structure estimation method(1). This corresponds to an atmospheric half-life of about 0.8 hours at an atmospheric concentration of 5X10+5 hydroxyl radicals per cu cm(1). Diclofenac is not expected to undergo hydrolysis in the environment due to the lack of hydrolyzable functional groups(2); no evidence of hydrolysis was observed in Lake Greifensee **water** samples following incubation in the dark for up to 37 days(4). Direct photolysis is the predominant removal process in freshwater, exhibiting an average elimination rate of 0.082/day, corresponding to a half-life of 8 days(3). Photodegradation experiments under laboratory conditions resulted in the formation of 3 photoproducts, 2 most likely being the methyl esters of **carbazole-1-acetic acid** and its 8-chloro derivative, the third being unidentified(4). Reduction of the compound by natural photolytic degradation may also be dependent on eutrophiic conditions, degree of solid particulate matter, and depth of watercourse(5). A photochemical half-life of 30 minutes was observed using Mississippi River **water**(6).

(1) Meylan WM, Howard PH; Chemosphere 26: 2293-99 (1993)

(2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 7-4, 7-5 (1990)

(3) Tixier C et al; Environ Sci Technol 37: 1061-68 (2003)

(4) Buser HR et al; Environ Sci Technol 32: 3449-56 (1998)

(5) Heberer T; in Amer Chem Soc, Div Environ Chem, Preprints 219th Mtg, 40: 192-4 (2002)

(6) Packer JL et al; Aquat Sci 65: 342-351 (2003)

▸ Hazardous Substances Data Bank (HSDB)

12.2.7 Environmental Bioconcentration

An estimated BCF of 3 was calculated for diclofenac(SRC), using a log Kow of 4.51(1) and a regression-derived equation(2). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is low(SRC), provided the compound is not altered physically or chemically once released into the environment.

(1) Avdeef A; Seminar on Ionization & Lipophilicity. Log P values measured by pION Inc., Brookline, MA. Avdeef A, Berger C, eds (1987)

(2) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999)

(3) Franke C et al; Chemosphere 29: 1501-14 (1994)

▸ Hazardous Substances Data Bank (HSDB)

12.2.8 Soil Adsorption / Mobility

Using an agricultural soil from Corrstown, County Dublin, Ireland a log Koc of 2.39 was measured(1), corresponding to a Koc of 245(SRC). According to a classification scheme(2), this estimated Koc value suggests that diclofenac is expected to have moderate mobility in soil. The pKa of diclofenac is 4.15(3), indicating that this compound will exist almost entirely in the dissociated form in the environment and anions generally do not adsorb more strongly to organic carbon and clay than their neutral counterparts(4). Adsorption to sediments from Lake Greifensee, Switzerland was found to be negligible(5). When 500 ng/L diclofenac was mixed with one liter of lake water and 1 g sediment/L water, the aqueous phase showed no decrease in concentration following centrifugation and removal of sediment particles(5).

(1) Barron L et al; Analyst 134: 663-670 (2009)

(2) Swann RL et al; Res Rev 85: 17-28 (1983)

(3) Sangster J; LOGKOW Databank. Sangster Res. Lab., Montreal Quebec, Canada (1994)

(4) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds. Boca Raton, FL: Lewis Publ (2000)

(5) Buser HR et al; Environ Sci Technol 32: 3449-56 (1998)

▸ Hazardous Substances Data Bank (HSDB)

12.2.9 Volatilization from Water / Soil

A pKa of 4.15(1) indicates diclofenac will exist almost entirely in the anion form at pH values of 5 to 9 and therefore volatilization from water and moist soil surfaces is not expected to be an important fate process. Diclofenac is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 6.1X10-8 mm Hg(SRC), determined from a fragment constant method(2).

(1) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991)

(2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990)

(3) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)

▸ Hazardous Substances Data Bank (HSDB)

12.2.10 Environmental Water Concentrations

GROUNDWATER: Diclofenac was detected at decreasing concentrations during artificial groundwater replenishment at a plant in Germany; concentrations started at 135 ng/L in the recharge pond, and

levels in down-gradient testing wells as follows: 15, 45, 5, 15, 10, <5, <5, 10 ng/L, not detected, not detected (detection limit not specified)(1). Diclofenac's mean removal rate of 93% was attributed to attenuation(1).

(1) Heberer T, Adam M; Environ Chem 1: 22-25 (2004)

▸ **Hazardous Substances Data Bank (HSDB)**

DRINKING WATER: Diclofenac was detected in influent water samples from 8 drinking water plants in France analyzed from March-April 2007, January 2008, and September-October 2008. Plant influent levels ranged from not detected to 35.0 ng/L; effluent concentrations ranged from not detected to 1.0 ng/L. The detection limit was 1.0 ng/L(1).

(1) Vulliet E et al; Environ Chem Lett 9: 103-114 (2011)

▸ **Hazardous Substances Data Bank (HSDB)**

SURFACE WATER: Diclofenac was detected in river water samples collected from the Aa Ulster and Aabach Moenchaltorf Rivers, Lake Greifensee region, Switzerland between August 16, 1999 and October 22, 1999 at maximum concentrations of 145 and 140 ng/L, respectively(1). It was detected in lake water samples collected from Lake Greifensee, Switzerland between August 16, 1999 and October 22, 1999 at a maximum concentration ranging of 7 ng/L at a depth of 20 meters(1). Daily influent loads of diclofenac into Lake Greifensee watershed, Switzerland averaged 9.254 g/day(1). Diclofenac was detected in 22 of 43 rivers and streams sampled in Germany at a median concentration of 0.15 ug/L, detection limit = 0.01 ug/L(2). Concentrations in the Rhine River at Mainz fluctuated throughout the year, with <0.1 ug/L detected in September, 1996 to a maximum of 0.66 ug/L detected in February, 1996(2). Diclofeniac transformation products 3'-hydroxydiclofenac and 8-chlorocarbazole-1-yl-ethanoic acid were detected at ranges of 0.08-0.3 ug/L and 0.03-0.4 ug/L, respectively, in Malir River and Lyari River water samples, near Karachi, Pakistan. Other transformation products identified were 4'- and 5'-hydroxydiclofenac and 1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indole-2-one at concentrations of 0.4-1.8, 0.01-0.3, and 0.02-0.3 ug/L, respectively. Sampling was conducted in December 2006 and April 2007(3). Average diclofenac concentrations in surface waters worldwide were as follows (ng/L): Austria, 190; Finland, 220; France, 300; Germany, 500; Netherlands 30; Switzerland, 80; UK, not reported; Canada, 120; USA, 30; Brazil, not reported, Japan, 5, Korea, 45(4). The concentration range in the River Elbe and its tributaries, Germany was reported as 10-50 ng/L, sampled in April 1998(5). Diclofenac concentrations remained fairly constant at 0.4 ug/L 0.493 to 194.8 km from a sewage treatment plant outfall in samples from Wascana Creek, Saskatchewan, Canada, tested in March 2005. It was not detected during July 200 6 sampling(6). The concentration of diclofenac in rivers sampled October 25-30, 2007 near Madrid Spain sampled downstream from major sewage treatment plants ranged from 313 to 3363 ng/L; median concentration was 2040 ng/L(7).

(1) Tixier C et al; Environ Sci Technol 37: 1061-68 (2003)

(2) Ternes TA; Wat Res 32: 3245-60 (1998)

(3) Scheurrell M et al; Chemosphere 77: 870-876 (2009)

(4) Zhang Y et al; Chemosphere 73: 1151-1161 (2008)

(5) Wiegel S et al; Chemosphere 57:107-126 (2004)

(6) Waiser MJ et al; Environ Toxicol Chem 30: 508-519 (2011)

(7) Valcarcel Yet al; Chemosphere 82: 1062-1071 (2011)

Hazardous Substances Data Bank (HSDB)

12.2.11 Effluent Concentrations

Samples of effluent from 18 sewage treatment plants in 14 municipalities in Canada were analyzed for the presence of neutral and acidic drugs over the period from September 1998 to February 1999(1). The median diclofenac influent concentration was 1.3 ug/L; the compound was not detected in any of the effluent samples, detection limit of 0.25 ug/L(1). Diclofenac was detected in effluents of three wastewater treatment plant samples collected in the region of Lake Greifensee, Switzerland between August 16, 1999 and October 22, 1999 at a maximum concentration of 0.99 ug/L(2). The compound was detected in 49 of 49 treatment plant effluents in Germany at a median concentration of 0.81 ug/L, detection limit = 0.05 ug/L(3). The compound was detected in wastewater treatment plant effluents in France, Greece, and Switzerland at a range of 0.25-5.45 ug/L, median of 0.47 ug/L; sampling conducted from February to March 2001(4). Diclofenac removal efficiencies from wastewater treatment plants ranges from 0 to 80% but fall mainly in the range of 21-40%. Average diclofenac concentrations in wastewater treatment plant effluents worldwide were as follows (ng/L): Austria, 1750; Denmark 950; Finland, 1000; France, 750; Germany, 3250; Greece, 750; Italy, 700; Spain, 600; Sweden, 800; Switzerland, 100; UK, not reported; Canada, 1400; USA, 200; Brazil, not reported, Japan, 50, Korea, 400(5). The estimated total discharge in 2002 from riverine, sewage treatment plants, and industrial sources in the Netherlands was 4.075 tons/year(6). Influent and effluent concentrations ranged from 112-438 ng/L (mean 286 ng/L) and 35.3 to 463 ng/L (mean 185 ng/L), respectively, in samples from 2 sewage treatment plants in Beijing, China, sampled monthly from February 2009-January 2010(7).

(1) Metcalfe CD et al; Environ Toxicol Chem 22: 2872-80 (2003)

(2) Tixier C et al; Environ Sci Technol 37: 1061-68 (2003)

(3) Ternes TA; Wat Res 32: 3245-60 (1998)

(4) Ferrari B et al; Ecotoxicol Environ Saf 55: 359-370 (2003)

(5) Zhang Y et al; Chemosphere 73: 1151-1161 (2008)

(6) Walraven N, Laane RWPM: Rev Environ Contam Toxicol 199: 1-18 (2008)

(7) Sui Q et al; Environ Sci Technol 45: 3341-3348 (2011)

Hazardous Substances Data Bank (HSDB)

12.2.12 Sediment / Soil Concentrations

SEDIMENT: Diclofenac was not detected in sediment samples collected from Lake Greifensee, Switzerland near the inflow of the River Aabach, which receives wastewater containing the compound(1).

(1) Buser HR et al; Environ Sci Technol 32: 3449-56 (1998)

Hazardous Substances Data Bank (HSDB)

12.2.13 Milk Concentrations

Diclofenac is distributed into breast milk. In one study, long-term use of 150 mg per day produced concentrations of 100 ng/g in the breast milk. An infant of 4 to 5 kg consuming one liter per day would therefore ingest approximately 0.03 mg/kg/day.

Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 381

▸ Hazardous Substances Data Bank (HSDB)

12.2.14 Probable Routes of Human Exposure

Occupational exposure to diclofenac may occur through dermal contact with this compound at workplaces where diclofenac is produced or used. Monitoring data indicate that the general population may be exposed to diclofenac via ingestion of drinking **water**, dermal contact with this compound, and pharmaceutical use of consumer products containing diclofenac. (SRC)

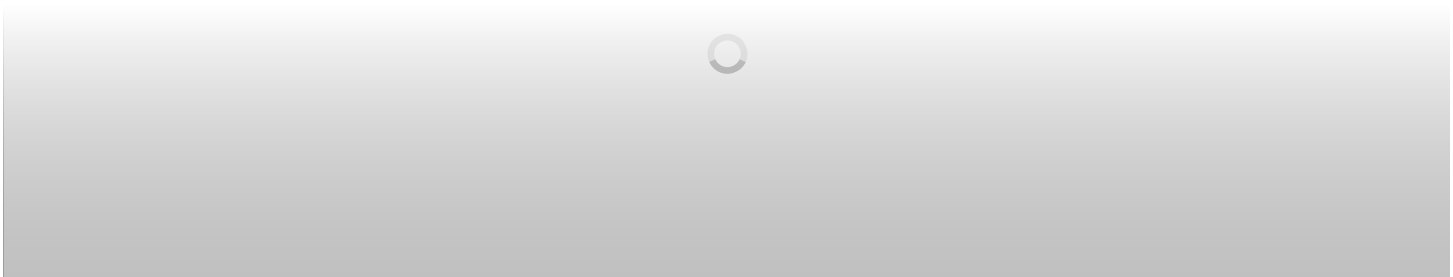
▸ Hazardous Substances Data Bank (HSDB)

13 Associated Disorders and Diseases

▸ Comparative Toxicogenomics Database (CTD); Open Targets; Therapeutic Target Database (TTD)

14 Literature

14.1 Consolidated References



PubChem

14.2 NLM Curated PubMed Citations

PubChem

14.3 Springer Nature References

Springer Nature

14.4 Thieme References

Thieme Chemistry

14.5 Wiley References

Wiley

14.6 Nature Journal References

Brosey et al. Chemical screening by time-resolved X-ray scattering to discover allosteric probes. Nature Chemical Biology, DOI: 10.1038/s41589-024-01609-1, published online 26 April 2024

Nature Chemical Biology

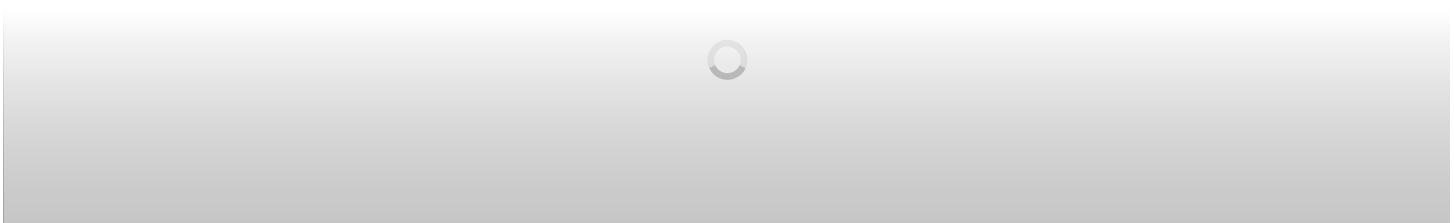
14.7 Chemical Co-Occurrences in Literature

PubChem

14.8 Chemical-Gene Co-Occurrences in Literature

PubChem

14.9 Chemical-Disease Co-Occurrences in Literature



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15 Patents

US6407079
US8217078
US8546450
US8618164
US8741956
US5985850
US5792753
US5914322
US5607690
US6974595
US7482377
US7759394
US8097651
US8927604
US6365180
US7662858
US7884095
US7939518
US8110606
US8623920
US6287594
US8946292
US9180095
US9186328
US8999387
US9173854
US9180096
US9017721
US8679544
US8252838
US8563613
US8871809
US9132110
US9220784
US9101591
US9168305
US9066913
US9168304
US9561200
US9370501
US9375412
US9339552
US9539335
US9415029
US9339551
US9827197
US11351133
US11344520

DrugBank

15.1 Depositor-Supplied Patent Identifiers

PubChem

Link to all deposited patent identifiers

▸ PubChem

15.2 WIPO PATENTSCOPE

Patents are available for this chemical structure:

https://patentscope.wipo.int/search/en/result.jsf?inchikey=DCOPUUMXTXDBNB-UHFFFAOYSA-N

▸ PATENTSCOPE (WIPO)

15.3 FDA Orange Book Patents

▸ FDA Orange Book

15.4 Chemical Co-Occurrences in Patents

PubChem

15.5 Chemical-Disease Co-Occurrences in Patents

PubChem

15.6 Chemical-Gene Co-Occurrences in Patents

PubChem

16 Interactions and Pathways

16.1 Protein Bound 3D Structures

▸ RCSB Protein Data Bank (RCSB PDB)

View 21 proteins in NCBI Structure

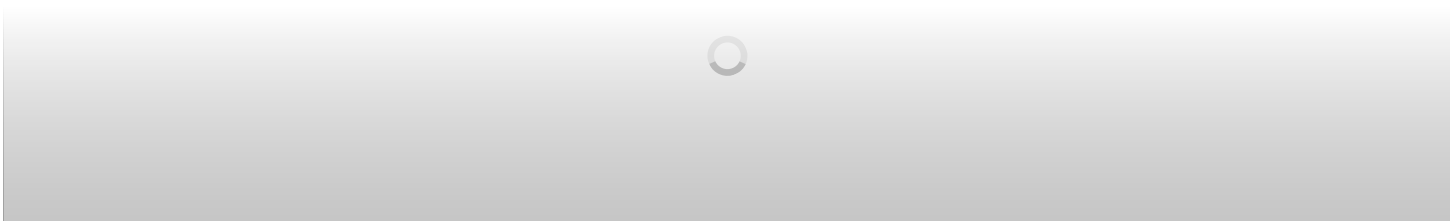
▸ PubChem

16.1.1 Ligands from Protein Bound 3D Structures

PDBe Ligand Code	DIF
PDBe Structure Code	1DVX
PDBe Conformer	

▸ Protein Data Bank in Europe (PDBe)

16.2 Chemical-Target Interactions



BindingDB; Comparative Toxicogenomics Database (CTD); Drug Gene Interaction database (DGIdb); IUPH…

DrugBank

16.3 Drug-Drug Interactions

DrugBank

16.4 Drug-Food Interactions

- Avoid excessive or chronic alcohol consumption. Co-administration with alcohol may increase the risk of gastrointestinal side effects, such as ulceration.
- Take with food. Food reduces gastric irritation.

▸ DrugBank

16.5 Pathways

▸ PubChem

17 Biological Test Results

17.1 BioAssay Results

PubChem

18 Taxonomy

Natural Product Activity and Species Source (NPASS)

19 Classification

19.1 MeSH Tree

Medical Subject Headings (MeSH)

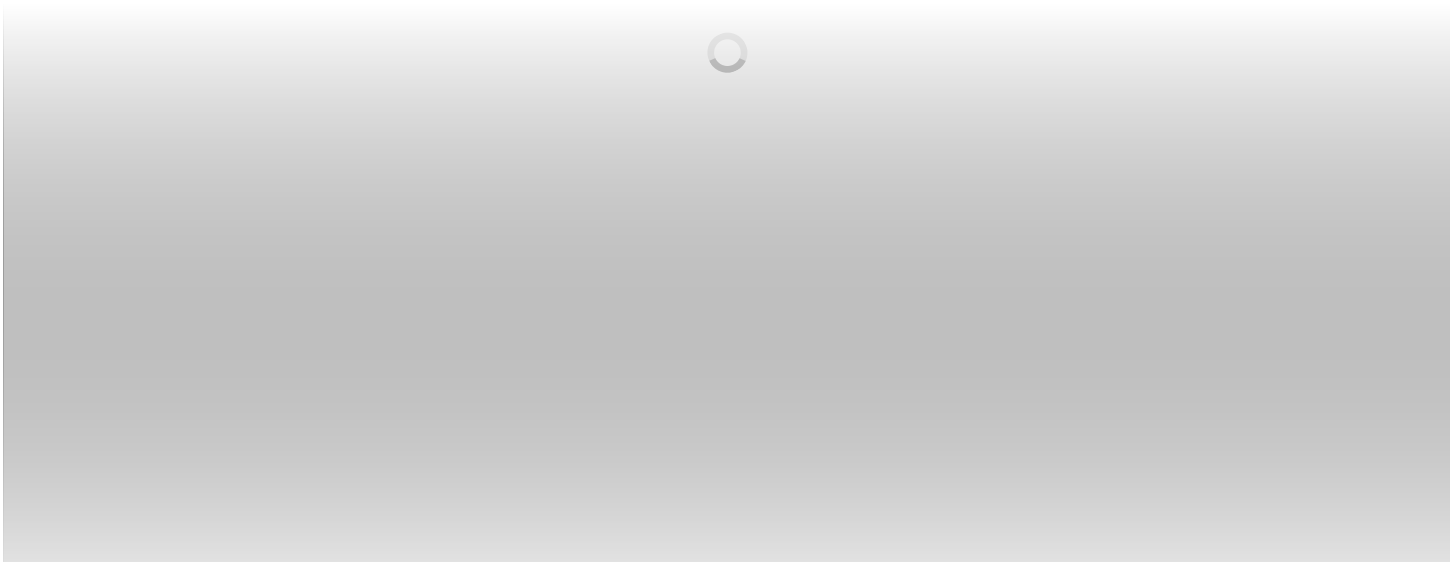
19.2 NCI Thesaurus Tree

NCI Thesaurus (NCIt)

19.3 ChEBI Ontology

ChEBI

19.4 KEGG: USP



KEGG

19.5 KEGG: ATC

KEGG

19.6 KEGG: Target-based Classification of Drugs

KEGG

19.7 KEGG: Risk Category of Japanese OTC Drugs

KEGG

19.8 KEGG: Drug Groups

KEGG

19.9 WHO ATC Classification System

▸ WHO Anatomical Therapeutic Chemical (ATC) Classification

19.10 FDA Pharm Classes

▸ FDA Pharm Classes

19.11 ChemIDplus

▸ ChemIDplus

19.12 IUPHAR / BPS Guide to PHARMACOLOGY Target Classification

▸ IUPHAR/BPS Guide to PHARMACOLOGY

19.13 ChEMBL Target Tree

▸ ChEMBL

19.14 UN GHS Classification

GHS Classification (UNECE)

19.15 EPA CPDat Classification

EPA Chemical and Products Database (CPDat)

19.16 NORMAN Suspect List Exchange Classification

NORMAN Suspect List Exchange

19.17 CCSBase Classification

CCSbase

19.18 EPA DSSTox Classification

EPA DSSTox

19.19 EPA Substance Registry Services Tree

EPA Substance Registry Services

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   https://services.industrialchemicals.gov.au/search-assessments/

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   https://www.drugbank.ca/drugs/DB00586

5. ### EPA DSSTox

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   https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

   Diclofenac
   https://comptox.epa.gov/dashboard/DTXSID6022923

   CompTox Chemicals Dashboard Chemical Lists
   https://comptox.epa.gov/dashboard/chemical-lists/

6. ### European Chemicals Agency (ECHA)

Diclofenac

https://chem.echa.europa.eu/100.035.755

2-((2,6-Dichlorophenyl)amino)benzeneacetic acid

https://echa.europa.eu/substance-information/-/substanceinfo/100.107.484

2-((2,6-Dichlorophenyl)amino)benzeneacetic acid (EC: 616-599-2)

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/6249

Diclofenac (EC: 239-348-5)

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/62870

7. FDA Global Substance Registration System (GSRS)

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https://gsrs.ncats.nih.gov/ginas/app/beta/substances/144O8QL0L1

8. Hazardous Substances Data Bank (HSDB)

DICLOFENAC

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http://www.hmdb.ca/metabolites/HMDB0014724

HMDB0014724_cms_27820

https://hmdb.ca/metabolites/HMDB0014724#spectra

10. BindingDB

2-{2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid

https://www.bindingdb.org/rwd/bind/chemsearch/marvin/MolStructure.jsp?monomerid=13066

11. Comparative Toxicogenomics Database (CTD)

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12. Drug Gene Interaction database (DGIdb)

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M8891

https://www.dgidb.org/drugs/iuphar.ligand:12714

13. IUPHAR/BPS Guide to PHARMACOLOGY

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https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=2714

Guide to Pharmacology Target Classification

https://www.guidetopharmacology.org/targets.jsp

14. Therapeutic Target Database (TTD)

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https://idrblab.net/ttd/data/drug/details/D0TG1H

15. Toxin and Toxin Target Database (T3DB)

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http://www.t3db.ca/downloads

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http://www.t3db.ca/toxins/T3D4729

16. CCSbase

CCSbase Classification

https://ccsbase.net/

17. NORMAN Suspect List Exchange

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NORMAN Suspect List Exchange Classification

https://www.norman-network.com/nds/SLE/

18. ChEBI

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https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:47381

ChEBI Ontology

http://www.ebi.ac.uk/chebi/userManualForward.do#ChEBI%20Ontology

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https://dailymed.nlm.nih.gov/dailymed/browse-drug-classes.cfm

FDA Pharmacological Classification

https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm

20. LiverTox

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https://ncit.nci.nih.gov

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> http://www.ebi.ac.uk/Information/termsofuse.html

https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL139/

ChEMBL Protein Target Tree

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https://www.crystallography.net/cod/2006252.html

https://www.crystallography.net/cod/2006253.html

https://www.crystallography.net/cod/2300059.html

26. The Cambridge Structural Database

https://www.ccdc.cam.ac.uk/structures/Search?Ccdcid=128771

https://www.ccdc.cam.ac.uk/structures/Search?Ccdcid=128772

https://www.ccdc.cam.ac.uk/structures/Search?Ccdcid=182858

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https://www.ccdc.cam.ac.uk/structures/Search?Ccdcid=251388

https://www.ccdc.cam.ac.uk/structures/Search?Ccdcid=665239

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https://www.ncbi.nlm.nih.gov/books/n/lactmed/LM89/

30. Drugs@FDA

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https://www.accessdata.fda.gov/scripts/cder/daf/

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https://comptox.epa.gov/dashboard/DTXSID6022923#exposure

EPA CPDat Classification

https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

32. EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/

33. FDA Medication Guides

Solaraze

https://dps.fda.gov/medguide

34. FDA Orange Book

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https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book

35. National Drug Code (NDC) Directory

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2-(2,6-DICHLOROANILINO)PHENYLACETIC ACID

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http://www.nist.gov/srd/nist1a.cfm

38. SpectraBase

Diclofenac -H2O (277)

https://spectrabase.com/spectrum/JolUAuY5v8c

Diclofenac

https://spectrabase.com/spectrum/5XL1A2udGpG

DCOPUUMXTXDBNB-UHFFFAOYSA-N

https://spectrabase.com/spectrum/8BZVzGLqW3g

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39. Japan Chemical Substance Dictionary (Nikkaji)

http://jglobal.jst.go.jp/en/redirect?Nikkaji_No=J8.557J

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https://www.kegg.jp/entry/C01690

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USP drug classification

http://www.genome.jp/kegg-bin/get_htext?br08302.keg

Anatomical Therapeutic Chemical (ATC) classification

http://www.genome.jp/kegg-bin/get_htext?br08303.keg

Target-based classification of drugs

http://www.genome.jp/kegg-bin/get_htext?br08310.keg

Risk category of Japanese OTC drugs

http://www.genome.jp/kegg-bin/get_htext?br08312.keg

Drug Groups

http://www.genome.jp/kegg-bin/get_htext?br08330.keg

41. Kruve Lab, Ionization & Mass Spectrometry, Stockholm University

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42. MassBank Europe

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NPC481151

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46. NIPH Clinical Trials Search of Japan

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ATC Code

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52. Protein Data Bank in Europe (PDBe)

http://www.ebi.ac.uk/pdbe-srv/pdbechem/chemicalCompound/show/DIF

53. RCSB Protein Data Bank (RCSB PDB)

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59. Medical Subject Headings (MeSH)

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https://www.ncbi.nlm.nih.gov/mesh/68004008

MeSH Tree

http://www.nlm.nih.gov/mesh/meshhome.html

Anti-Inflammatory Agents, Non-Steroidal

https://www.ncbi.nlm.nih.gov/mesh/68000894

Cyclooxygenase Inhibitors

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GHS Classification Tree

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62. EPA Substance Registry Services

EPA SRS List Classification

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63. PATENTSCOPE (WIPO)

SID 403461915

https://pubchem.ncbi.nlm.nih.gov/substance/403461915

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