[Template:Bots](/wiki/Template:Bots" \o "Template:Bots) [Template:Drugbox](/wiki/Template:Drugbox) **Paracetamol**, also known as **acetaminophen** or **APAP**, is a medication used to treat [pain](/wiki/Pain) and [fever](/wiki/Fever).<ref name=AHFS2016/> It is typically used for mild to moderate pain.<ref name=AHFS2016/> There is poor evidence for fever relief in children.[[1]](#cite_note-1) It is often sold in combination with other ingredients such as in many [cold medications](/wiki/Cold_medication).<ref name=AHFS2016/> In combination with [opioid pain medication](/wiki/Opioid_analgesic), paracetamol is used for more severe pain such as [cancer pain](/wiki/Cancer_pain) and after surgery.[[2]](#cite_note-2) It is typically used either by mouth or [rectally](/wiki/Rectally) but is also available [intravenously](/wiki/Intravenously).<ref name=AHFS2016/><ref name=Hoch2014/> Effects last between two and four hours.<ref name=Hoch2014/>

Paracetamol is generally safe at recommended doses.[[3]](#cite_note-3) Serious skin rashes may rarely occur, and too high a dose can result in [liver failure](/wiki/Liver_failure).<ref name=AHFS2016/> It appears to be safe during [pregnancy](/wiki/Pregnancy) and when [breastfeeding](/wiki/Breastfeeding).<ref name=AHFS2016>[Template:Cite web](/wiki/Template:Cite_web)</ref> In those with liver disease, it may still be used, but lower doses should be taken.[[4]](#cite_note-4) Paracetamol is classified as a mild [analgesic](/wiki/Analgesic).<ref name=Hoch2014>[Template:Cite book](/wiki/Template:Cite_book)</ref> It does not have significant [anti-inflammatory](/wiki/Anti-inflammatory) activity and how it works is not entirely clear.[[5]](#cite_note-5) Paracetamol was discovered in 1877.[[6]](#cite_note-6) It is the most commonly used medication for pain and fever in both the United States and Europe.[[7]](#cite_note-7) It is on the [WHO Model List of Essential Medicines](/wiki/WHO_Model_List_of_Essential_Medicines), the most important medications needed in a basic [health system](/wiki/Health_system).[[8]](#cite_note-8) Paracetamol is available as a [generic medication](/wiki/Generic_medication) with trade names including [*Tylenol*](/wiki/Tylenol_(brand)) and [*Panadol*](/wiki/Panadol_(brand)) among others.[[9]](#cite_note-9) The wholesale price in the [developing world](/wiki/Developing_world) is less than 0.01 USD per dose.[[10]](#cite_note-10) In the United States it costs about 0.04 USD per dose.[[11]](#cite_note-11)[Template:TOC limit](/wiki/Template:TOC_limit)

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## Medical uses[[edit](/index.php?title=(none)&action=edit&section=1)]

### Fever[[edit](/index.php?title=(none)&action=edit&section=2)]

Paracetamol is used for reducing [fever](/wiki/Fever) in people of all ages.<ref name=AHFS>[Template:Cite web](/wiki/Template:Cite_web)</ref> The [World Health Organization](/wiki/World_Health_Organization) (WHO) recommends that paracetamol be used to treat fever in children only if their temperature is greater than [Template:Convert](/wiki/Template:Convert).[[12]](#cite_note-12) The efficacy of paracetamol by itself in children with fevers has been questioned[[13]](#cite_note-13) and a meta-analysis showed that it is less effective than [ibuprofen](/wiki/Ibuprofen).[[14]](#cite_note-14)

### Pain[[edit](/index.php?title=(none)&action=edit&section=3)]

Paracetamol is used for the relief of mild to moderate pain. The use of the intravenous form for pain of sudden onset in people in the emergency department is supported by limited evidence.[[15]](#cite_note-15)

#### Osteoarthritis[[edit](/index.php?title=(none)&action=edit&section=4)]

The [American College of Rheumatology](/wiki/American_College_of_Rheumatology) recommends paracetamol as one of several treatment options for people with arthritis pain of the hip, hand, or knee that does not improve with exercise and weight loss.[[16]](#cite_note-16) A 2015 review, however, found it provided only a small benefit in osteoarthritis.<ref name=BMJ2015>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Paracetamol has relatively little anti-inflammatory activity, unlike other common analgesics such as the [NSAIDs](/wiki/Non-steroidal_anti-inflammatory_drug) aspirin and ibuprofen, but ibuprofen and paracetamol have similar effects in the treatment of headache. Paracetamol can relieve pain in mild arthritis, but has no effect on the underlying inflammation, redness, and swelling of the joint.[[17]](#cite_note-17) It has [analgesic](/wiki/Analgesic) properties comparable to those of [aspirin](/wiki/Aspirin), while its anti-inflammatory effects are weaker. It is better tolerated than aspirin due to concerns with bleeding with aspirin.

#### Low back pain[[edit](/index.php?title=(none)&action=edit&section=5)]

Based on a systematic review, paracetamol is recommended by the [American College of Physicians](/wiki/American_College_of_Physicians) and the [American Pain Society](/wiki/American_Pain_Society) as a first-line treatment for low back pain.[[18]](#cite_note-18)[[19]](#cite_note-19) However other systematic reviews concluded that evidence for its efficacy is lacking.<ref name=BMJ2015/>[[20]](#cite_note-20)

#### Headaches[[edit](/index.php?title=(none)&action=edit&section=6)]

A joint statement of the German, Austrian, and Swiss headache societies and the German Society of Neurology recommends the use of paracetamol in combination with caffeine as one of several first line therapies for treatment of tension or migraine headache.[[21]](#cite_note-21) In the treatment of acute migraine, it is superior to placebo, with 39% of people experiencing pain relief at 1 hour compared to 20% in the control group.[[22]](#cite_note-22)

#### Postoperative pain[[edit](/index.php?title=(none)&action=edit&section=7)]

Paracetamol, when combined with NSAIDs, may be more effective for treating postoperative pain than either paracetamol alone or NSAIDs alone.[[23]](#cite_note-23)

#### Other[[edit](/index.php?title=(none)&action=edit&section=8)]

The efficacy of paracetamol when used in combination with weak opioids (such as [codeine](/wiki/Codeine)) improved for approximately 50% of people but with increases in the number experiencing side effects.[[24]](#cite_note-24)[[25]](#cite_note-25) Combination drugs of paracetamol and strong opioids like morphine improve analgesic effect.[[26]](#cite_note-26) The combination of paracetamol with caffeine is superior to paracetamol alone for the treatment of common pain conditions including dental pain, postpartum pain, and headache.[[27]](#cite_note-27)

## Adverse effects[[edit](/index.php?title=(none)&action=edit&section=9)]

Healthy adults taking regular doses of up to 4,000 mg a day show little evidence of toxicity (although some researchers disagree). They are more likely to have abnormal liver function tests, but the significance of this is uncertain.<ref name=BMJ2015/>

### Liver damage[[edit](/index.php?title=(none)&action=edit&section=10)]

Acute [overdoses](/wiki/Overdose) of paracetamol can cause potentially fatal [liver damage](/wiki/Hepatotoxicity). In 2011 the US [Food and Drug Administration](/wiki/Food_and_Drug_Administration) launched a public education program to help consumers avoid overdose, warning: "Acetaminophen can cause serious liver damage if more than directed is used."[[28]](#cite_note-28)[[29]](#cite_note-29)[[30]](#cite_note-30) In a 2011 Safety Warning the FDA immediately required manufacturers to update labels of all prescription combination acetaminophen products to warn of the potential risk for severe liver injury and required such combinations contain no more than 325 mg of acetaminophen (within 3 years).[[31]](#cite_note-31)[[32]](#cite_note-32) FDA has likewise requested prescribers limit combination opioids to 325 mg of acetaminophen. Such overdoses are frequently related to high dose [recreational use](/wiki/Recreational_drug_use) of prescription [opioid](/wiki/Opioid)s as these opioids are most often combined with acetaminophen.[[33]](#cite_note-33) The overdose risk may be heightened by frequent consumption of alcohol.

[Paracetamol toxicity](/wiki/Paracetamol_toxicity) is the foremost cause of [acute liver failure](/wiki/Acute_liver_failure) in the [Western world](/wiki/Western_world), and accounts for most drug overdoses in the United States, the United Kingdom, Australia and New Zealand.[[34]](#cite_note-34)[[35]](#cite_note-35)[[36]](#cite_note-36)[[37]](#cite_note-37) According to the FDA, in the United States there were "56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths per year related to acetaminophen-associated overdoses during the 1990s. Within these estimates, unintentional acetaminophen overdose accounted for nearly 25 percent of the emergency department visits, 10 percent of the hospitalizations, and 25 percent of the deaths."[[38]](#cite_note-38) Paracetamol is metabolised by the liver and is [hepatotoxic](/wiki/Hepatotoxic); side effects are multiplied when combined with alcoholic drinks, and are very likely in [chronic alcoholics](/wiki/Alcoholism) or patients with liver damage.[[39]](#cite_note-39)[[40]](#cite_note-40) Some studies have suggested the possibility of a moderately increased risk of upper gastrointestinal complications such as [stomach bleeding](/wiki/Upper_gastrointestinal_bleeding) when high doses are taken chronically.[[41]](#cite_note-41) [Kidney damage](/wiki/Kidney_damage) is seen in rare cases, most commonly in overdose.[[42]](#cite_note-42)

### Skin reactions[[edit](/index.php?title=(none)&action=edit&section=11)]

On August 2, 2013, the U.S. [Food and Drug Administration](/wiki/Food_and_Drug_Administration) (FDA) issued a new warning about paracetamol. It stated that the drug could cause rare, and possibly fatal, skin reactions, such as [Stevens–Johnson syndrome](/wiki/Stevens–Johnson_syndrome) and [toxic epidermal necrolysis](/wiki/Toxic_epidermal_necrolysis). Prescription-strength products will be required to carry a warning label about skin reactions, and the FDA has urged manufacturers to do the same with over-the-counter products.[[43]](#cite_note-43)

### Asthma[[edit](/index.php?title=(none)&action=edit&section=12)]

There is an association between paracetamol use and [asthma](/wiki/Asthma) but the evidence suggests that this likely reflects confounders<ref name=Henderson>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> rather than a causal role.[[44]](#cite_note-44) A 2014 review found that among children the association disappeared when respiratory infections were taken into account.[[45]](#cite_note-45) As of 2014, the [American Academy of Pediatrics](/wiki/American_Academy_of_Pediatrics) and the [National Institute for Health and Care Excellence](/wiki/National_Institute_for_Health_and_Care_Excellence) (NICE) continue to recommend paracetamol for pain and discomfort in children,[[46]](#cite_note-46)[[47]](#cite_note-47)[[48]](#cite_note-48)[[49]](#cite_note-49)[[50]](#cite_note-50)[[51]](#cite_note-51) but some experts have recommended that paracetamol use by children with asthma, or at risk for asthma, should be avoided.<ref name=Martinez>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[52]](#cite_note-52)

### Other factors[[edit](/index.php?title=(none)&action=edit&section=13)]

In contrast to aspirin, paracetamol does not prevent blood from clotting (it is not an [antithrombotic](/wiki/Antithrombotic)), and thus may be used in patients where failure of blood [coagulation](/wiki/Coagulation) is a concern; and it does not cause gastric irritation.[[53]](#cite_note-53) However, paracetamol does not help reduce inflammation, while aspirin does.[[54]](#cite_note-54) Compared to [ibuprofen](/wiki/Ibuprofen)—whose side effects may include diarrhea, vomiting and abdominal pain—paracetamol has fewer adverse gastrointestinal effects.[[55]](#cite_note-55) Unlike aspirin, paracetamol is generally considered safe for children, as it is not associated with a risk of [Reye's syndrome](/wiki/Reye's_syndrome) in children with viral illnesses.[[56]](#cite_note-56) But if taken recreationally with opioids, there is weak evidence that it may cause hearing loss.[[57]](#cite_note-57)

### Overdose[[edit](/index.php?title=(none)&action=edit&section=14)]

[Template:Main article](/wiki/Template:Main_article)

Untreated paracetamol overdose results in a lengthy, painful illness. Signs and symptoms of paracetamol toxicity may initially be absent or [non-specific symptoms](/wiki/Non-specific_symptom). The first symptoms of overdose usually begin several hours after ingestion, with [nausea](/wiki/Nausea), [vomiting](/wiki/Vomiting), sweating, and [pain](/wiki/Pain) as [acute liver failure](/wiki/Acute_liver_failure) starts.[[58]](#cite_note-58) People who take overdoses of paracetamol do not fall asleep or lose consciousness, although most people who attempt suicide with paracetamol wrongly believe that they will be rendered unconscious by the drug.[[59]](#cite_note-59) The process of dying from an overdose takes between 3–5 days to 4–6 weeks.

Paracetamol hepatotoxicity is, by far, the most common cause of acute liver failure in both the United States and the United Kingdom.[[37]](#cite_note-37)[[60]](#cite_note-60) Paracetamol overdose results in more calls to [poison control centers](/wiki/Poison_control_center) in the US than overdose of any other pharmacological substance.[[61]](#cite_note-61) Toxicity of paracetamol is believed to be due to its [quinone metabolite](/wiki/1,4-Benzoquinone).[[62]](#cite_note-62) Untreated overdose can lead to [liver failure](/wiki/Liver_failure) and death within days. Treatment is aimed at removing the paracetamol from the body and replacing [glutathione](/wiki/Glutathione).[[62]](#cite_note-62) [Activated charcoal](/wiki/Activated_charcoal) can be used to decrease absorption of paracetamol if the patient presents for treatment soon after the overdose. While the antidote, [acetylcysteine](/wiki/Acetylcysteine) (also called N-acetylcysteine or NAC), acts as a precursor for glutathione, helping the body regenerate enough to prevent or at least decrease the possible damage to the liver, a [liver transplant](/wiki/Liver_transplant) is often required if damage to the liver becomes severe.[[34]](#cite_note-34)[[63]](#cite_note-63) NAC was usually given following a treatment [nomogram](/wiki/Nomogram) (one for patients with risk factors, and one for those without) but the use of the nomogram is no longer recommended as evidence to support the use of risk factors was poor and inconsistent, and many of the risk factors are imprecise and difficult to determine with sufficient certainty in clinical practice.[[64]](#cite_note-64) NAC also helps in neutralizing the imidoquinone metabolite of paracetamol.[[62]](#cite_note-62) [Kidney failure](/wiki/Kidney_failure) is also a possible side effect.

There were tablets available until 2004 (brand-name in the UK Paradote) that combined paracetamol with an antidote ([methionine](/wiki/Methionine)), to protect the liver in case of an overdose. One theoretical, but rarely if ever used, option in the United States is to request a [compounding pharmacy](/wiki/Compounding_pharmacy) to make a similar drug mix for at-risk patients.

In June 2009, a [U.S. Food and Drug Administration](/wiki/Food_and_Drug_Administration_(United_States)) (FDA) advisory committee recommended that new restrictions should be placed on paracetamol usage in the United States to help protect people from the potential toxic effects. The maximum dosage at any given time would be decreased from 1000 mg to 650 mg, while combinations of paracetamol and [opioid](/wiki/Opioid) [analgesics](/wiki/Analgesic) would be prohibited. Committee members were particularly concerned by the fact that the present maximum dosages of paracetamol had been shown to produce alterations in [hepatic](/wiki/Liver) function.[[65]](#cite_note-65) In January 2011, the FDA asked manufacturers of prescription combination products containing paracetamol to limit the amount of paracetamol to no more than 325 mg per tablet or capsule and began requiring manufacturers to update the labels of all prescription combination paracetamol products to warn of the potential risk of severe liver damage.[[66]](#cite_note-66)[[67]](#cite_note-67)[[68]](#cite_note-68)[[69]](#cite_note-69) Manufacturers had three years to limit the amount of paracetamol in their prescription drug products to 325 mg per dosage unit.[[67]](#cite_note-67)[[69]](#cite_note-69)In November 2011, the [Medicines and Healthcare products Regulatory Agency](/wiki/Medicines_and_Healthcare_products_Regulatory_Agency) revised UK dosing of liquid paracetamol for children.[[70]](#cite_note-70)

### Pregnancy[[edit](/index.php?title=(none)&action=edit&section=15)]

Experimental studies in animals and cohort studies in humans indicate no detectable increase in congenital malformations associated with paracetamol use during [pregnancy](/wiki/Pregnancy).[[71]](#cite_note-71) Additionally, paracetamol does not affect the closure of the fetal [ductus arteriosus](/wiki/Ductus_arteriosus) as NSAIDs can.[[72]](#cite_note-72) Paracetamol use by the mother during pregnancy is associated with an increased risk of childhood [asthma](/wiki/Asthma).[[73]](#cite_note-73) It is also associated with an increase in [ADHD](/wiki/ADHD) but it is unclear whether the relationship is causal.[[74]](#cite_note-74) Despite these concerns, paracetamol remains the recommended medication for pain and fever during pregnancy.[[75]](#cite_note-75)

### Cancer[[edit](/index.php?title=(none)&action=edit&section=16)]

Some studies have found an association between paracetamol and a slight increase in [kidney cancer](/wiki/Renal_cell_carcinoma),[[76]](#cite_note-76) but does not affect [bladder cancer](/wiki/Bladder_cancer) risk.[[77]](#cite_note-77)

## Chemical properties[[edit](/index.php?title=(none)&action=edit&section=17)]

[thumb|Paracetamol molecule](/wiki/Image:Polar-surface-area.png) [polar surface area](/wiki/Polar_surface_area)[Template:Citation needed](/wiki/Template:Citation_needed) [thumb|Paracetamol electron map electrostatic surface area](/wiki/Image:Paracetamol_Electron_Map.png)[Template:Citation needed](/wiki/Template:Citation_needed)

Paracetamol consists of a [benzene](/wiki/Benzene) ring core, [substituted](/wiki/Substituent) by one [hydroxyl](/wiki/Hydroxyl) group and the [nitrogen](/wiki/Nitrogen) atom of an [amide](/wiki/Amide) group in the *para* (1,4) [pattern](/wiki/Arene_substitution_patterns).[[78]](#cite_note-78) The amide group is [acetamide](/wiki/Acetamide) (ethanamide). It is an extensively [conjugated system](/wiki/Conjugated_system), as the [lone pair](/wiki/Lone_pair) on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the [p orbital](/wiki/Atomic_orbital) on the [carbonyl](/wiki/Carbonyl) carbon, and the lone pair on the carbonyl oxygen are all conjugated. The presence of two activating groups also make the benzene ring highly reactive toward [electrophilic](/wiki/Electrophile) aromatic substitution. As the substituents are *ortho, para*-directing and *para* with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the [basicity](/wiki/Base_(chemistry)) of the oxygens and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the [phenoxide](/wiki/Phenol) [anion](/wiki/Ion).

Paracetamol is part of the class of drugs known as "[aniline](/wiki/Aniline) analgesics"; it is the only such drug still in use today.[[79]](#cite_note-79) It is not considered an NSAID because it does not exhibit significant anti-inflammatory activity (it is a weak COX inhibitor).[[80]](#cite_note-80)[[81]](#cite_note-81) This is despite the evidence that paracetamol and NSAIDs have some similar pharmacological activity.[[82]](#cite_note-82)

## Mechanism of action[[edit](/index.php?title=(none)&action=edit&section=18)]

[thumb|](/wiki/Image:AM404_skel.svg)[AM404](/wiki/AM404) – [Metabolite](/wiki/Metabolite) of paracetamol [thumb|](/wiki/Image:Anandamide_skeletal.svg)[Anandamide](/wiki/Anandamide) – Endogenous [cannabinoid](/wiki/Cannabinoid)

To date, the mechanism of action of paracetamol is not completely understood. The main mechanism proposed is the inhibition of [cyclooxygenase](/wiki/Cyclooxygenase) (COX), and recent findings suggest that it is highly selective for [COX-2](/wiki/COX-2).[[83]](#cite_note-83) Because of its selectivity for COX-2 it does not significantly inhibit the production of the pro-clotting [thromboxanes](/wiki/Thromboxane).[[83]](#cite_note-83) While it has [analgesic](/wiki/Analgesic) and [antipyretic](/wiki/Antipyretic) properties comparable to those of [aspirin](/wiki/Aspirin) or other [NSAIDs](/wiki/NSAID), its peripheral anti-inflammatory activity is usually limited by several factors, one of which is the high level of [peroxides](/wiki/Peroxides) present in [inflammatory](/wiki/Inflammation) lesions. However, in some circumstances, even peripheral anti-inflammatory activity comparable to [NSAIDs](/wiki/NSAID) can be observed.

An article[[84]](#cite_note-84) in Nature Communications from researchers in London, UK and Lund, Sweden in November 2011 has found a hint to the analgesic mechanism of paracetamol, being that the metabolites of paracetamol e.g. [NAPQI](/wiki/NAPQI), act on [TRPA1-receptors](/wiki/Transient_receptor_potential_cation_channel,_member_A1) in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain.

This conclusion has been contested in a new hypothesis paper<ref name=Claesson>[Template:Cite web](/wiki/Template:Cite_web)</ref> on how paracetamol might act. The author concedes that [NAPQI](/wiki/NAPQI) is the active metabolite but that this reactive compound should react not only with the thiol in TRPA1 but also with any other suitably available nucleophile that it happens to encounter. It is suggested that thiol groups in cysteine proteases, e.g. the proteases that take part in the processing of procytokines, such as those generating [IL-1β](/wiki/Interleukin_1_family) and [IL-6](/wiki/Interleukin-6), might be the targets giving rise to overall analgesic effects.

The COX family of enzymes are responsible for the metabolism of [arachidonic acid](/wiki/Arachidonic_acid) to [prostaglandin H2](/wiki/Prostaglandin_H2), an unstable molecule that is, in turn, converted to numerous other pro-inflammatory compounds. Classical anti-inflammatories such as the [NSAIDs](/wiki/NSAID) block this step. Only when appropriately oxidised is the COX enzyme highly active.[[85]](#cite_note-85)[[86]](#cite_note-86) Paracetamol reduces the oxidised form of the COX enzyme, preventing it from forming pro-inflammatory chemicals.[[87]](#cite_note-87)[[88]](#cite_note-88) This leads to a reduced amount of *prostaglandin E2* in the CNS, thus lowering the hypothalamic set-point in the thermoregulatory centre.

Aspirin is known to inhibit the [cyclooxygenase](/wiki/Cyclooxygenase) (COX) family of enzymes and, because paracetamol's action is partially similar to aspirin's,[Template:Clarify](/wiki/Template:Clarify) much research has focused on whether paracetamol also inhibits COX. It is now clear that paracetamol acts via at least two pathways.[[79]](#cite_note-79)[[87]](#cite_note-87)[[89]](#cite_note-89)[[90]](#cite_note-90) The exact mechanisms by which COX is inhibited in various circumstances are still a subject of discussion. Because of differences in the activity of paracetamol, aspirin, and other NSAIDs, it has been postulated that further COX variants may exist. One theory holds that paracetamol works by inhibiting the [COX-3](/wiki/COX-3) isoform—a COX-1 [splice variant](/wiki/Splice_variant)—of the COX family of enzymes.[[83]](#cite_note-83) When expressed in dogs, this enzyme shares a strong similarity to the other COX enzymes, produces pro-inflammatory chemicals, and is selectively inhibited by paracetamol.[[91]](#cite_note-91) However, some research has suggested that, in humans and mice, the COX-3 enzyme is without inflammatory action and paracetamol's blockage of it is not significant in its functioning in humans.[[83]](#cite_note-83)[[89]](#cite_note-89) Another possibility is that paracetamol blocks cyclooxygenase (as in aspirin), but that, in an inflammatory environment where the concentration of peroxides is high, the high oxidation state of paracetamol prevents its actions. This idea would mean that paracetamol has no direct effect at the site of inflammation, but instead acts in the CNS where the environment is not oxidative, to reduce temperature, etc.[[91]](#cite_note-91) Paracetamol also modulates the [endogenous cannabinoid system](/wiki/Endocannabinoid_system).[[92]](#cite_note-92) Paracetamol is metabolised to [AM404](/wiki/AM404), a compound with several actions; what is most important is that it inhibits the reuptake of the endogenous cannabinoid/vanilloid [anandamide](/wiki/Anandamide) by neurons. Anandamide reuptake lowers synaptic levels of anandamide and results in more activation of the main pain receptor (nociceptor) of the body, the [TRPV1](/wiki/TRPV1) (older name: vanilloid receptor). By inhibiting anandamide reuptake, levels in the synapse remain high and are able to desensitise the TRPV1 receptor much like [capsaicin](/wiki/Capsaicin). Furthermore, AM404 inhibits sodium channels, as do the anesthetics [lidocaine](/wiki/Lidocaine) and [procaine](/wiki/Procaine).[[93]](#cite_note-93) Both of these actions by themselves have been shown to reduce pain, and are a possible mechanism for paracetamol. It has been demonstrated that when cannabinoid receptors are blocked with synthetic antagonists, paracetamol's analgesic effects are prevented, suggesting its pain-relieving action involves the endogenous cannabinoid system.[[94]](#cite_note-94) Spinal [TRPA1](/wiki/TRPA1) receptors have also been demonstrated to mediate antinociceptive effects of paracetamol and Δ9-tetrahydrocannabinol in mice.[[95]](#cite_note-95) Increase of social behavior in mice dosed with paracetamol (which corresponds to a reduction of [social rejection](/wiki/Social_rejection) response in humans) does not appear to be due to [cannabinoid receptor type 1](/wiki/Cannabinoid_receptor_type_1) activity. It may result from [serotonin receptor](/wiki/Serotonin_receptor) [agonism](/wiki/Receptor_agonist).[[96]](#cite_note-96)

## Pharmacokinetics[[edit](/index.php?title=(none)&action=edit&section=19)]

[thumb|Main pathways of paracetamol metabolism *(click to enlarge)*. Pathways shown in blue and purple lead to non-toxic metabolites; the pathway in red leads to toxic](/wiki/Image:Paracetamol_metabolism.svg) [NAPQI](/wiki/NAPQI).

After oral administration it is rapidly absorbed by the GI tract; its volume of distribution is roughly 50 L.[[97]](#cite_note-97) The concentration in serum after a typical dose of paracetamol usually peaks below 30 µg/ml, which equals 200 µmol/L.<ref name=rosen/> After 4 hours the concentration is usually less than 10 µg/mL, which equals 66 µmol/L.<ref name=rosen>[Template:Cite book](/wiki/Template:Cite_book)</ref>

Paracetamol is [metabolised](/wiki/Drug_metabolism) primarily in the [liver](/wiki/Liver), into toxic and non-toxic products. Three [metabolic pathways](/wiki/Metabolic_pathway) are notable:[[62]](#cite_note-62)\*[Glucuronidation](/wiki/Glucuronidation) (45-55%),<ref name = TGA/> by [UGT1A1](/wiki/UDP_glucuronosyltransferase_1_family,_polypeptide_A1) and [UGT1A6](/wiki/UDP_glucuronosyltransferase_1_family,_polypeptide_A1);[[77]](#cite_note-77)\*Sulfation (sulfate conjugation) (20–30%)<ref name = TGA/> by [SULT1A1](/wiki/SULT1A1);[[77]](#cite_note-77)\**N*-hydroxylation and dehydration, then GSH conjugation, (less than 15%). The hepatic [cytochrome P450](/wiki/Cytochrome_P450) enzyme system metabolises paracetamol, forming a minor yet significant alkylating metabolite known as [NAPQI](/wiki/NAPQI) (*N*-acetyl-*p*-benzoquinone imine) (also known as *N*-acetylimidoquinone).[[62]](#cite_note-62)[[98]](#cite_note-98) NAPQI is then irreversibly conjugated with the [sulfhydryl groups](/wiki/Thiol) of [glutathione](/wiki/Glutathione).[[98]](#cite_note-98) All three pathways yield final products that are inactive, non-toxic, and eventually excreted by the kidneys. In the third pathway, however, the intermediate product NAPQI is toxic. NAPQI is primarily responsible for the [toxic effects](/wiki/#Toxicity) of paracetamol; this constitutes an example of [toxication](/wiki/Toxication).<ref name = MD/> Production of NAPQI is due primarily to two [isoenzymes](/wiki/Isoenzyme) of cytochrome P450: [CYP2E1](/wiki/CYP2E1)[[77]](#cite_note-77) and [CYP3A4](/wiki/CYP3A4).<ref name = MD>[Template:Cite web](/wiki/Template:Cite_web)</ref> At usual doses, NAPQI is quickly detoxified by conjugation with glutathione.[[62]](#cite_note-62)[[98]](#cite_note-98)

## Synthesis[[edit](/index.php?title=(none)&action=edit&section=20)]

### Original (Boots) method[[edit](/index.php?title=(none)&action=edit&section=21)]

The original method for production involves the [nitration](/wiki/Nitration) of [phenol](/wiki/Phenol) with [sodium nitrate](/wiki/Sodium_nitrate) gives a mixture of two isomers, from which the wanted [4-nitrophenol](/wiki/4-nitrophenol) (bp 279 °C) can easily be separated by [steam distillation](/wiki/Steam_distillation). In this [electrophilic aromatic substitution](/wiki/Electrophilic_aromatic_substitution) reaction, phenol's oxygen is strongly activating, thus the reaction requires only mild conditions as compared to nitration of benzene itself. The [nitro group](/wiki/Nitro_group) is then reduced to an amine, giving [4-aminophenol](/wiki/4-aminophenol). Finally, the amine is acetylated with [acetic anhydride](/wiki/Acetic_anhydride).[[99]](#cite_note-99) Industrially direct hydrogenation is used, but in the laboratory scale sodium borohydride serves.[[100]](#cite_note-100)<ref name = Ullmann/>

[500px](/wiki/Image:Synthesis_of_paracetamol_from_phenol.svg)

### Green(er) synthesis[[edit](/index.php?title=(none)&action=edit&section=22)]

An alternative industrial synthesis developed by [Hoechst](/wiki/Hoechst_AG)–[Celanese](/wiki/Celanese) involves direct acylation of phenol with acetic anhydride catalyzed by HF, conversion of the ketone to a [ketoxime](/wiki/Ketoxime) with [hydroxylamine](/wiki/Hydroxylamine), followed by the acid-catalyzed [Beckmann rearrangement](/wiki/Beckmann_rearrangement) to give the amide.<ref name = Ullmann>[Template:Ullmann](/wiki/Template:Ullmann)</ref>[[101]](#cite_note-101)

[475px](/wiki/File:Celanese_synthesis_of_paracetamol.svg)

### Direct synthesis[[edit](/index.php?title=(none)&action=edit&section=23)]

More recently (2014) a "one-pot" synthesis from [hydroquinone](/wiki/Hydroquinone) has been described before the Royal Society of Chemistry.[[102]](#cite_note-102)[[103]](#cite_note-103) The process may be summarized as follows:

Hydroquinone, [ammonium acetate](/wiki/Ammonium_acetate), and [acetic acid](/wiki/Acetic_acid) are mixed in an argon atmosphere and heated slowly to 230 °C. The mixture was stirred at this temperature for 15 hours. After cooling the acetic acid was evaporated and the precipitate was filtered, washed with water and dried to give paracetamol as a white solid.

The authors go on to claim an 88% yield and 99% purity.

## Reactions[[edit](/index.php?title=(none)&action=edit&section=24)]

[*4*-Aminophenol](/wiki/4-Aminophenol) may be obtained by the amide [hydrolysis](/wiki/Hydrolysis) of paracetamol. *4*-Aminophenol prepared this way, and related to the commercially available [Metol](/wiki/Metol), has been used as a developer in photography by hobbyists.[[104]](#cite_note-104) This reaction is also used to determine paracetamol in urine samples: After hydrolysis with hydrochloric acid, *4*-aminophenol reacts in ammonia solution with a phenol derivate, e.g. salicylic acid, to form an [indophenol](/wiki/Indophenol) dye under oxidization by air.[[105]](#cite_note-105)

## History[[edit](/index.php?title=(none)&action=edit&section=25)]

[thumb|](/wiki/Image:Axelrod.jpg)[Julius Axelrod](/wiki/Julius_Axelrod) *(pictured)* and [Bernard Brodie](/wiki/Bernard_Brodie_(biochemist)) demonstrated that acetanilide and phenacetin are both metabolised to paracetamol, which is a better tolerated analgesic.

[Acetanilide](/wiki/Acetanilide) was the first [aniline](/wiki/Aniline) derivative serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced into medical practice under the name of [Antifebrin](/wiki/Antifebrin) by A. Cahn and P. Hepp in 1886.[[106]](#cite_note-106) But its unacceptable toxic effects, the most alarming being [cyanosis](/wiki/Cyanosis) due to [methemoglobinemia](/wiki/Methemoglobinemia), prompted the search for less toxic aniline derivatives.[[79]](#cite_note-79) [Harmon Northrop Morse](/wiki/Harmon_Northrop_Morse) had already synthesised paracetamol at [Johns Hopkins University](/wiki/Johns_Hopkins_University) via the reduction of [*p*-nitrophenol](/wiki/4-Nitrophenol) with [tin](/wiki/Tin) in glacial [acetic acid](/wiki/Acetic_acid) in 1877,[[107]](#cite_note-107)<ref name=badmed/> but it was not until 1887 that clinical pharmacologist [Joseph von Mering](/wiki/Joseph_von_Mering) tried paracetamol on patients.[[79]](#cite_note-79) In 1893, von Mering published a paper reporting on the clinical results of paracetamol with [phenacetin](/wiki/Phenacetin), another aniline derivative.[[108]](#cite_note-108) Von Mering claimed that, unlike phenacetin, paracetamol had a slight tendency to produce methemoglobinemia. Paracetamol was then quickly discarded in favor of phenacetin. The sales of phenacetin established [Bayer](/wiki/Bayer) as a leading pharmaceutical company.<ref name=drugdiscov>[Template:Cite book](/wiki/Template:Cite_book)</ref> Overshadowed in part by [aspirin](/wiki/Aspirin), introduced into medicine by [Heinrich Dreser](/wiki/Heinrich_Dreser) in 1899, phenacetin was popular for many decades, particularly in widely advertised over-the-counter "headache mixtures", usually containing phenacetin, an [aminopyrine](/wiki/Aminopyrine) derivative of aspirin, caffeine, and sometimes a [barbiturate](/wiki/Barbiturate).[[79]](#cite_note-79) Paracetamol is the active metabolite of [phenacetin](/wiki/Phenacetin) and [acetanilide](/wiki/Acetanilide), both once popular as analgesics and antipyretics in their own right.[[97]](#cite_note-97)[[109]](#cite_note-109) However, unlike phenacetin, acetanilide and their combinations, paracetamol is not considered [carcinogenic](/wiki/Carcinogen) at therapeutic doses.<ref name=Bergman>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Von Mering's claims remained essentially unchallenged for half a century, until two teams of researchers from the United States analyzed the metabolism of acetanilide and paracetamol.<ref name=drugdiscov/> In 1947 [David Lester](/wiki/David_Lester_(biochemist)) and Leon Greenberg found strong evidence that paracetamol was a major metabolite of acetanilide in human blood, and in a subsequent study they reported that large doses of paracetamol given to albino rats did not cause methemoglobinemia.[[110]](#cite_note-110) In three papers published in the September 1948 issue of the [*Journal of Pharmacology and Experimental Therapeutics*](/wiki/Journal_of_Pharmacology_and_Experimental_Therapeutics), [Bernard Brodie](/wiki/Bernard_Brodie_(biochemist)), [Julius Axelrod](/wiki/Julius_Axelrod) and Frederick Flinn confirmed using more specific methods that paracetamol was the major metabolite of acetanilide in human blood, and established that it was just as efficacious an analgesic as its precursor.[[111]](#cite_note-111)[[112]](#cite_note-112)[[113]](#cite_note-113) They also suggested that methemoglobinemia is produced in humans mainly by another metabolite, [phenylhydroxylamine](/wiki/Phenylhydroxylamine). A follow-up paper by Brodie and Axelrod in 1949 established that phenacetin was also metabolised to paracetamol.[[114]](#cite_note-114) This led to a "rediscovery" of paracetamol.[[79]](#cite_note-79) It has been suggested that contamination of paracetamol with [4-aminophenol](/wiki/4-aminophenol), the substance von Mering synthesised it from, may be the cause for his spurious findings.<ref name=drugdiscov/>

Paracetamol was first marketed in the United States in 1950 under the name Triagesic, a combination of paracetamol, [aspirin](/wiki/Aspirin), and [caffeine](/wiki/Caffeine).<ref name=badmed/> Reports in 1951 of three users stricken with the blood disease [agranulocytosis](/wiki/Agranulocytosis) led to its removal from the marketplace, and it took several years until it became clear that the disease was unconnected.<ref name=badmed/> Paracetamol was marketed in 1953 by [Sterling-Winthrop Co.](/wiki/Sterling-Winthrop_Co.) as Panadol, available only by prescription, and promoted as preferable to aspirin since it was safe for children and people with ulcers.[[115]](#cite_note-115) In 1955, paracetamol was marketed as Children's [Tylenol](/wiki/Tylenol) Elixir by [McNeil Laboratories](/wiki/McNeil_Laboratories).[[116]](#cite_note-116) In 1956, 500 [mg](/wiki/Milligram) tablets of paracetamol went on sale in the United Kingdom under the trade name Panadol, produced by Frederick Stearns & Co, a subsidiary of [Sterling Drug](/wiki/Sterling_Drug) Inc. In 1963, paracetamol was added to the [*British Pharmacopoeia*](/wiki/British_Pharmacopoeia), and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents.<ref name=badmed>[Template:Cite book](/wiki/Template:Cite_book)</ref> Concerns about paracetamol's safety delayed its widespread acceptance until the 1970s, but in the 1980s paracetamol sales exceeded those of aspirin in many countries, including the United Kingdom. This was accompanied by the commercial demise of phenacetin, blamed as the cause of [analgesic nephropathy](/wiki/Analgesic_nephropathy) and hematological toxicity.[[79]](#cite_note-79) In 1988 [Sterling Winthrop](/wiki/Sterling_Winthrop) was acquired by [Eastman Kodak](/wiki/Eastman_Kodak) which sold the over the counter drug rights to [SmithKline Beecham](/wiki/SmithKline_Beecham) in 1994.[[117]](#cite_note-117) Available [without a prescription](/wiki/Over-the-counter_drug) since 1959,[[118]](#cite_note-118) it has since become a common household drug.[[119]](#cite_note-119) [Patents](/wiki/Patent) on paracetamol have long expired, and generic versions of the drug are widely available.<ref name=drugs.com-internatl/>[[120]](#cite_note-120)

## Society and culture[[edit](/index.php?title=(none)&action=edit&section=26)]

### Naming[[edit](/index.php?title=(none)&action=edit&section=27)]

Acetaminophen is the name generally used in the United States ([USAN](/wiki/United_States_Adopted_Name)), Japan ([JAN](/wiki/Japanese_Accepted_Name)), Canada[[121]](#cite_note-121) Venezuela, Colombia.,<ref name=INN2007/> and Iran; paracetamol is used in international venues ([INN](/wiki/International_Nonproprietary_Name), [AAN](/wiki/Australian_Approved_Name), [BAN](/wiki/British_Approved_Name)).[[121]](#cite_note-121)[[122]](#cite_note-122)[[123]](#cite_note-123) In some contexts, such as on prescription bottles of painkillers that incorporate this medicine, it is simply abbreviated as APAP, for **a**cetyl-**p**ara-**a**mino**p**henol.

Both acetaminophen and paracetamol come from a chemical name for the compound: *para*-**acet**yl**aminophen**ol and ***par****a*-**acet**yl**am**inophen**ol**.

### Available forms[[edit](/index.php?title=(none)&action=edit&section=28)]

[Template:See also](/wiki/Template:See_also) [Template:Multiple image](/wiki/Template:Multiple_image)

Paracetamol is available in a [tablet](/wiki/Tablet_(pharmacy)), [capsule](/wiki/Capsule_(pharmacy)), liquid suspension, [suppository](/wiki/Suppository), [intravenous](/wiki/Intravenous), [intramuscular](/wiki/Intramuscular) and [effervescent](/wiki/Effervescent) form. The common adult dose is 500 mg to 1000 mg. The recommended maximum daily dose, for adults, is 4000 mg. In recommended doses, paracetamol is generally safe for children and infants, as well as for adults,[[124]](#cite_note-124) although rare cases of acute liver injury have been linked to amounts lower than 2500 mg per day.[[125]](#cite_note-125) In some formulations, paracetamol is combined with the [opioid](/wiki/Opioid) [codeine](/wiki/Codeine), sometimes referred to as [co-codamol](/wiki/Co-codamol) ([BAN](/wiki/British_Approved_Name)) and Panadeine in Australia. In the U.S., this combination is available only by prescription, while the lowest-strength preparation is over-the-counter in Canada, and, in other countries, other strengths may be available over the counter.[Template:Citation needed](/wiki/Template:Citation_needed) Paracetamol is also combined with other opioids such as [dihydrocodeine](/wiki/Dihydrocodeine), referred to as [co-dydramol](/wiki/Co-dydramol) ([BAN](/wiki/British_Approved_Name)), [oxycodone](/wiki/Oxycodone) or [hydrocodone](/wiki/Hydrocodone). Another very commonly used analgesic combination includes paracetamol in combination with [propoxyphene napsylate](/wiki/Propoxyphene_napsylate). A combination of paracetamol, codeine, and the calmative [doxylamine succinate](/wiki/Doxylamine) is also available. The efficacy of paracetamol/codeine combinations have been questioned by recent research.<ref name=nps01>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Paracetamol is commonly used in multi-ingredient preparations for [migraine](/wiki/Migraine) headache, typically including [butalbital](/wiki/Butalbital) and paracetamol with or without [caffeine](/wiki/Caffeine), and sometimes containing codeine.

Paracetamol is sometimes combined with [phenylephrine hydrochloride](/wiki/Phenylephrine_hydrochloride).[[126]](#cite_note-126) Sometimes a third active ingredient, such as [ascorbic acid](/wiki/Ascorbic_acid),[[126]](#cite_note-126)[[127]](#cite_note-127) [caffeine](/wiki/Caffeine),[[128]](#cite_note-128)[[129]](#cite_note-129) [chlorpheniramine maleate](/wiki/Chlorphenamine),[[130]](#cite_note-130) or [guaifenesin](/wiki/Guaifenesin)[[131]](#cite_note-131)[[132]](#cite_note-132)[[133]](#cite_note-133) is added to this combination.

When marketed in combination with [diphenhydramine hydrochloride](/wiki/Diphenhydramine_hydrochloride), it is frequently given the label "PM" and is meant as a sleep aid. Diphenhydramine hydrochloride is known to have hypnotic effects and is non-habit forming. Unfortunately it has been implicated in the occasional development of [restless leg syndrome](/wiki/Restless_leg_syndrome).[[134]](#cite_note-134)

### Controversy[[edit](/index.php?title=(none)&action=edit&section=29)]

In September 2013 an episode of [*This American Life*](/wiki/This_American_Life) entitled "Use Only as Directed"[[135]](#cite_note-135) highlighted deaths from Paracetamol overdose. This report was followed by two reports by [ProPublica](/wiki/ProPublica)[[136]](#cite_note-136)[[137]](#cite_note-137) alleging that the "FDA has long been aware of studies showing the risks of acetaminophen. So has the maker of Tylenol, McNeil Consumer Healthcare, a division of Johnson & Johnson" and "McNeil, the maker of Tylenol, ... has repeatedly opposed safety warnings, dosage restrictions and other measures meant to safeguard users of the drug."

A report prepared by an internal FDA working group describes a history of FDA initiatives designed to educate consumers about the risk of paracetamol overdose, and notes that one challenge to the Agency has been "identifying the appropriate message about the relative safety of acetaminophen, especially compared to other OTC pain relievers (e.g., aspirin and other NSAIDs)". The report notes that "Chronic use of NSAIDs is also associated with significant morbidity and mortality. NSAID gastrointestinal risk is substantial, with deaths and hospitalization estimated in one publication as 3200 and 32,000 per year respectively. Possible cardiovascular toxicity with chronic NSAID use has been a major discussion recently", finally noting that "The goal of the educational efforts is not to decrease appropriate acetaminophen use or encourage substitution of NSAID use, but rather to educate consumers so that they can avoid unnecessary health risks."[[138]](#cite_note-138)

## Veterinary use[[edit](/index.php?title=(none)&action=edit&section=30)]

### Cats[[edit](/index.php?title=(none)&action=edit&section=31)]

Paracetamol is extremely toxic to cats, which lack the necessary [glucuronyl transferase](/wiki/Glucuronyl_transferase) enzymes to break it down safely. Initial symptoms include vomiting, salivation, and discoloration of the tongue and gums.

Unlike an overdose in humans, liver damage is rarely the cause of death; instead, [methemoglobin](/wiki/Methemoglobin) formation and the production of [Heinz bodies](/wiki/Heinz_bodies) in red blood cells inhibit oxygen transport by the blood, causing [asphyxiation](/wiki/Asphyxiation) ([methemoglobemia](/wiki/Methemoglobemia) and [hemolytic anemia](/wiki/Hemolytic_anemia)).[[139]](#cite_note-139) Treatment with [N-acetylcysteine](/wiki/N-acetylcysteine),[[140]](#cite_note-140) [methylene blue](/wiki/Methylene_blue) or both is sometimes effective after the ingestion of small doses of paracetamol.

### Dogs[[edit](/index.php?title=(none)&action=edit&section=32)]

Although paracetamol is believed to have no significant anti-inflammatory activity, it has been reported as effective as aspirin in the treatment of musculoskeletal pain in dogs.<ref name=smallani>[Template:Cite book](/wiki/Template:Cite_book)</ref>

A paracetamol-codeine product (trade name Pardale-V)[[141]](#cite_note-141) licensed for use in dogs is available on veterinary prescription in the UK.[[141]](#cite_note-141) It should be administered to dogs only on veterinary advice and with extreme caution.[[141]](#cite_note-141) The main effect of toxicity in dogs is liver damage, and GI ulceration has been reported.[[140]](#cite_note-140)[[142]](#cite_note-142)[[143]](#cite_note-143)[[144]](#cite_note-144) N-acetylcysteine treatment is efficacious in dogs when administered within a 2 hours of paracetamol ingestion.[[140]](#cite_note-140)<ref name=smallani/>

### Snakes[[edit](/index.php?title=(none)&action=edit&section=33)]

Paracetamol is also lethal to snakes, and has been suggested as a chemical control program for the invasive [brown tree snake](/wiki/Brown_tree_snake) (*Boiga irregularis*) in [Guam](/wiki/Guam).[[145]](#cite_note-145)[[146]](#cite_note-146) Doses of 80 mg are inserted into dead mice scattered by helicopter.[[147]](#cite_note-147)

## References[[edit](/index.php?title=(none)&action=edit&section=34)]

[Template:Reflist](/wiki/Template:Reflist)

## External links[[edit](/index.php?title=(none)&action=edit&section=35)]

[Template:Commons category](/wiki/Template:Commons_category)

* [Template:Portal-inline](/wiki/Template:Portal-inline)
* [Paracetamol at Chemsynthesis](http://www.chemsynthesis.com/base/chemical-structure-18651.html)
* [Paracetamol International Chemical Safety Cards](http://www.cdc.gov/niosh/ipcsneng/neng1330.html)
* [The Julius Axelrod Papers](http://profiles.nlm.nih.gov/HH/Views/Exhibit/narrative/amines.html)
* [FDA: Safe Use of Over-the-Counter Pain Relievers/Fever Reducers](http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/SafeUseofOver-the-CounterPainRelieversandFeverReducers/ucm164977.htm)
* [FDA: Consumer Update "Acetaminophen and Liver Injury: Q and A for Consumers" (link)](http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm168830.htm)
* [FDA: Consumer Update "Acetaminophen and Liver Injury: Q and A for Consumers" (PDF)](http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM172664.pdf)
* [U.S. National Library of Medicine: Drug Information Portal–Paracetamol](http://druginfo.nlm.nih.gov/drugportal/dpdirect.jsp?name=Acetaminophen)
* [Acetaminophen bound to proteins](http://www.ebi.ac.uk/pdbe-srv/PDBeXplore/ligand/?ligand=TYL) in the [PDB](/wiki/Protein_Data_Bank)

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[Category:Acetanilides](/wiki/Category:Acetanilides) [Category:Analgesics](/wiki/Category:Analgesics) [Category:Antipyretics](/wiki/Category:Antipyretics) [Category:Endocannabinoid reuptake inhibitors](/wiki/Category:Endocannabinoid_reuptake_inhibitors) [Category:Phenols](/wiki/Category:Phenols) [Category:Drugs with unknown mechanisms of action](/wiki/Category:Drugs_with_unknown_mechanisms_of_action) [Category:World Health Organization essential medicines](/wiki/Category:World_Health_Organization_essential_medicines) [Category:RTT](/wiki/Category:RTT)