Pindone

(CAS No: 83-26-1)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

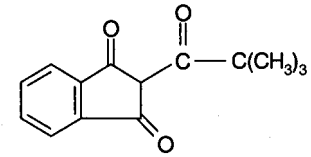
The present document contains the assessment of the health hazard of pindone by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by C de Heer, Ph.D and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, The Netherlands).

The evaluation of the toxicity of pindone has been based on the review by American Conference of Governmental Industrial Hygienists (ACGIH) (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in June 1997, literature was searched in the on-line databases Medline, Cancerlit, Toxline, and Chemical Abstracts covering the period 1966 to 30 June 1997, 1963 to 18 June 1997, 1965 to 21 March 1997, and 1967 to 1 July 1997, respectively, and using the following key words: pindone, pival, 2-pivalyl-1,3-indandione, and 83-26-1. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO97, NLM97).

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland) and P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz and Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

An additional literature search in Toxline and Medline in September 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	pindone
synonyms	:	2-pivaloylindan-1,3-dione; 2-(2,2-dimethyl-1-oxopropyl)-1*H*-indene-1,3(2*H*)-dione; pival; 2-pivalyl-1,3-indandione; pivaldione; pivalyn; 2-trimethylacetyl-1,3-indandione; pivacin; pivalyl valone; tri-ban; chemrat
molecular formula	:	$C_{14}H_{14}O_3$
structural formula	:	
CAS number	:	83-26-1

Data from ACG91, NLM97, Ric94.

3 Physical and chemical properties

molecular weight	:	230.25
boiling point	:	180ºC
melting point	:	108.5-110.5ºC
flash point	:	not available
vapour pressure	:	not available
solubility in water	:	not soluble (at 25ºC: 18 mg/L)
log $P_{octanol/water}$	:	2.87 (estimated)
conversion factors	:	not applicable

Data from ACG91, Ric94, http://esc.syrres.com.

Pindone is a bright yellow crystalline material with almost no odour (ACG91). The very slight odour present is characterised as slightly mouldy and acrid suggestive of marigolds (Lis71).

4 Uses

Pindone is an anticoagulant rodenticide that blocks (vitamin K-dependent) prothrombin formation. It is also used as an insecticide and in organic synthesis (ACG91, Ric94).

According to the database of the Dutch Pesticide Authorisation Board (CTB)*, pindone is at present not permitted in the Netherlands for use as an active ingredient in pesticides.

5 Biotransformation and kinetics

In general, 1,3-indandione derivatives are not absorbed after inhalation exposure, and they do not penetrate the skin (NLM97).

The pharmacokinetics of a single dose of 3 and 5 mg/kg pindone after oral and intravenous administration were investigated in dogs. The results of both routes of administration fitted on a one-compartment open model. After oral administration, 67% of the dose was absorbed. The elimination half-life was approximately 5 days. The delayed elimination was ascribed to a strong binding to plasma protein (98%), a wide distribution in the organism, a nearly complete renal reabsorption at physiological pH, and a lack of metabolic conversion to more polar compounds (Fit78).

Puppies of an Alsatian intoxicated with the pindone containing rodenticide formulation Actosin P® (concentration not indicated) showed plasma concentrations of pindone ranging from 1.3 to 2.0 µg/mL. In the liver, the concentrations ranged from 1.1 to 1.7 µg/g tissue. In the mother, plasma levels of pindone were 1.4 µg/mL (blood sampled 1 day post-partum). The results point to a passage of pindone through the placental barrier. Rodenticide concentrations observed in the puppies were mostly higher than those in the mother, suggesting an even lesser ability of the newborn to metabolise or excrete these drugs (Fit77, NLM97).

6 Effects and mechanism of action

Human data

Acute clinical effects after accidental pindone exposure depend on the side of bleeding and include haemoptysis, haematuria, gastrointestinal bleeding, abdominal or back pain (retroperitioneal haemorrhage), haemarthrosis, epistaxis, cerebrovascular accidents, and multiple ecchymotic lesions (NLM97).

The occurrence of granulocytosis and hepatitis has been reported in some patients treated with phenindione (2-phenylindan-1,3-dione), which is based on the same chemical structure as pindone. There is little experience with pindone,

* At: http://www.ctb-wageningen.nl.

although clinical use of indandiones has shown diarrhoea, pyrexia, renal tubular necrosis, paralysis of accommodation, and exfoliative dermatitis to occur (ACG91).

Animal data

Pindone is a vitamin K antagonist, with delayed inhibition of prothrombin formation, and repeated doses having a cumulative effect on blood coagulation (ACG91). It depresses the hepatic synthesis of vitamin K_1-dependent clotting factors (II, VII, IX, X) by inhibiting the vitamin K_1 2,3-reductase enzyme in the vitamin K_1-epoxide cycle (NLM97).

Clinical signs of pindone intoxication relate to massive haemorrhages and include bloody discharge from body orifices, visible haematomas under the skin and around joints, purpura, dyspnoea, weakness, and signs of shock (NLM97). Indandiones cause symptoms and signs of neurological and cardiopulmonary injury in laboratory rats. These often lead to death before haemorrhages occur (NLM97). Prothrombin depression will occur in response to doses much lower than those necessary to cause haemorrhage (NLM97).

Acute toxicity data reported include oral LD_{50} values of 280 mg/kg for male Sherman rats (Gai69) and 75-100 mg/kg for dogs (Oli78). Deaths occurred in 2/3 dogs 6-7 days after single oral dosing of 5 mg/kg pindone (the third animal was saved from death by vitamin K treatment), whereas no mortality was observed after dosing of 3 mg/kg. Based on these observations, the oral LD_{50} for dogs was estimated to be 4 mg/kg (Fit78). The lowest lethal dose to Sherman rats was 200 mg/kg (Gai69). In wild (by-hand-caught) rats, i.e., Norway rats (*Rattus norvegicus*) and roof rats (*Rattus rattus*), the critical doses (defined as the smallest average dose killing a species so rapidly that the upper 95% confidence limit for that and higher average doses is 45 days or less) were estimated to be 10.3 and 17.0 mg/kg, respectively (Hay59). The intravenous LD_{50} for rats (strain not specified) was 50 mg/kg bw (Ric94). Single intraperitoneal injections of 10, 25, or 50 mg/kg into male Wistar rats caused 0, 17, and 42% mortality, respectively (Sau55).

The critical rodenticidal dose of pindone for house mice is 4.3 mg/kg. In rats, the ingestion of a single large dose of pindone causes rapid death due to pulmonary and visceral congestion without haemorrhage, and the mechanism of this acute reaction may not be related to vitamin K antagonism (ACG91).

Following repeated exposures for 5 days, LD_{50}s of 1.34 and 12.80 mg/kg were reported for inbred Sprague-Dawley and wild (*Rattus norvegicus*) rats, respectively (WHO95).

Daily oral dosing of 0.3 to 2.5 mg/kg pindone for 4-5 consecutive days to dogs, goats, cats, cattle, horses, and chickens caused a significant prolongation of prothrombin time in all species except the horse. The half-lives of elevated prothrombin time were calculated as 1.9 to 3.1 days. No clinical signs of anti-coagulant poisoning were observed (Mar91, Mar92).

Exposure of rabbits to 25 mg/kg pindone significantly reduced the mean haematocrit on day 6 after single oral dosing. Moreover, the one-stage prothrombin time and the activated partial prothrombin time were significantly increased (Eas93).

In one study, the toxicity of single and multiple doses of pindone to rabbits and sheep were compared. Deaths occurred at single oral (gavage) exposures to dose levels of 6.6 and 75 mg/kg bw in rabbits and sheep, respectively. The LD_{50} for a 7-days daily exposure to pindone, impregnated in oats, in rabbits was 0.52 mg/kg bw/day. Animals died 7-10 days after the first dose because of widespread haemorrhage throughout the muscles and some organs. None of 10 sheep exposed to a mean daily dose of 12 mg/kg (range 4.4-16 mg/kg) of pindone, impregnated in oats, for 7 days died or displayed signs of haemorrhage (Oli78).

Pindone was administered orally in gelatine capsules to broiler chickens. Graded levels of 0-500 mg/bird produced a dose-dependent increase in prothrombin time 20 hours after dosing. Statistical significance was observed at 4 mg/bird, and the maximum response level was reached at 16 mg/bird. The prothrombin time continued to rise from the 20th through the 32nd hour after dosing (Cha66).

Following 5 daily intraperitoneal injections of 5 mg/kg, 76% of the rats (male, Wistar) died within 7 days (Sau55).

The committee did not find data from studies on (sub)chronic toxicity, including carcinogenicity, of pindone.

Mutagenicity and genotoxicity

Pindone (0.1-100 µg/plate, purity >97%) was negative in mutagenicity tests in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation (Zei87). As reported in an (English) abstract (of a paper in Italian), commercial-grade pindone (purity not indicated) produced a statistically significant increase in the frequency of sex chromosome loss in male germ cells of *D. melanogaster*, but not in sex-linked recessive lethals (San93).

Reproduction toxicity

Puppies of an Alsatian intoxicated by the rodenticide Actosin P® (comprising warfarin and pindone; exposure level not indicated) a few days before term were either stillborn or died within the first hour post-partum. Autopsies showed severe haemorrhages in nearly all organs (Fit77). Abortion may occur in cattle (NLM97).

The committee did not find data from reproduction toxicity studies on pindone.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for pindone in the Netherlands is 0.1 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for pindone in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find human data from which an inhalation exposure concentration-effect relation can be estimated, or data from bioavailability studies.

Based on the elimination half-life of approximately 5 days observed in dogs after oral exposure, pindone may accumulate in the body. Pindone can cross the placental barrier.

LD_{50} values for acute oral toxicity data in rats ranged from 10.3 to 280 mg/kg bw and in dogs from 75-100 mg/kg bw. Studies on acute toxicity after dermal or inhalation exposure or on sensitisation were not available.

Repeated dosing of 0.3 mg/kg bw pindone for 4-7 days to various species resulted in significantly increased prothrombin times. Death in animals from chronic exposure is due to multiple internal haemorrhages. The oral LD_{50} for a 7-days daily pindone exposure in rabbits was 0.52 mg/kg bw.

Pindone was negative in mutagenicity test in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation. It induced an increase in the frequency of sex chromosome loss in male germ cells of *D. melanogaster*, but was negative in the sex-linked recessive lethal assay. No other data were available.

The committee did not find data from studies on (sub)chronic toxicity, including carcinogenicity, and reproduction toxicity of pindone.

The committee considers the toxicological database on pindone too poor to justify recommendation of a health-based occupational exposure limit.

Considering the 7-day LD_{50} of 0.52 mg/kg bw/day in rabbits (equivalent to a dose of 36.4 mg/day for workers, assuming an average body weight of 70 kg) and the present MAC-value of 0.1 mg/m^3, 8-hour TWA, (equivalent to a dose of 1 mg/day for workers, assuming a respiratory volume of 10 m^3 per working day), the committee has reason to believe that the present MAC-value is too high.

References

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Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

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TRG00 TRGS 900: Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe; BArbBl 2000; 2.

WHO95 World Health Organization (WHO): International Programme on Chemical Safety (IPCS). Antiocoagulant rodenticides. Geneva, Switzerland: WHO, 1995; Environmental Health Criteria 175.

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Annex

Occupational exposure limits for pindone in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	0.1	8 h	administrative		SZW03
Germany						
- AGS	-	0.1[c]	8 h			TRG00
- DFG MAK-Kommission	-	-				DFG03
Great-Britain						
- HSE	-	-			-	HSE02
Sweden	-	-				Swe00
Denmark	-	-				Arb02
USA						
- ACGIH	-	0.1	8 h	TLV		ACG03b
- OSHA	-	0.1	8 h	PEL		ACG03a
- NIOSH	-	0.1	10 h	REL		ACG03a
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] The inhalable fraction of the aerosol.