

PENTOSAN POLYSULFATE SODIUM

1. Exposure Data

In this *Monograph*, pentosan polysulfate sodium will also be referred to as pentosan.

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 37319-17-8; 140207-93-8

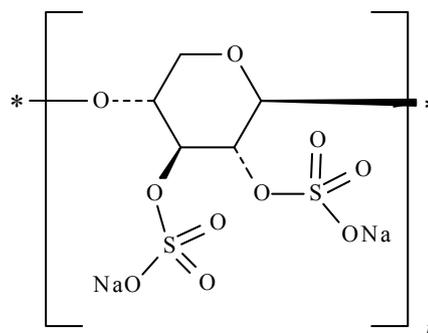
Chem. Abstr. Serv. Name: Xylan hydrogen sulfate, sodium salt ([SciFinder, 2010](#))

IUPAC systematic name: [(2*R*,3*R*,4*S*,5*R*)-2-hydroxy-5-[(2*S*,3*R*,4*S*,5*R*)-5-hydroxy-3,4-disulfoxyoxan-2-yl]oxy-3-sulfoxyoxan-4-yl] hydrogen sulfate, sodium ([PubChem, 2013](#))

Synonyms: Pentosan polysulfate sodium; Pentosan; Xylan hydrogen sulfate sodium salt; Xylan polysulfate sodium; Sodium pentosan polysulfate; Sodium pentosane polysulfate; Xylan sulfate sodium; Xylofuranan sulfate sodium; (1→4)-β-D-Xylan 2,3-bis(hydrogen sulfate) sodium; Sodium xylan polysulfate ([O'Neil, 2006](#); [SciFinder, 2010](#))

Proprietary names: Elmiron, Cartrophen, Fibrase, Fibrenzym, Hemoclar, SP-54, Thrombocid

1.1.2 Structural and molecular formulae and relative molecular mass



$(C_5H_6Na_2O_{10}S_2)_n$ where $n = 6-12$ ([US Pharmacopeial Convention, 2013](#))

Relative molecular mass: $[336]_n$

1.1.3 Chemical and physical properties of the pure substance

Description: White, odourless powder, slightly hygroscopic ([O'Neil, 2006](#))

Density: 1.344 at 20 °C, 10% aqueous solution ([O'Neil, 2006](#))

Spectroscopy data: Index of refraction is -57° at 20 °C ([O'Neil, 2006](#))

Solubility: Soluble in water to 50% at pH 6.0 ([O'Neil, 2006](#); [RxList, 2013](#))

1.1.4 Technical products and impurities

Pentosan polysulfate sodium is a plant-derived, semi-synthetic mucopolysaccharide with radiochemical purity of 95.6%, with no single major impurity ([Simon et al., 2005](#); [RxList, 2013](#)).

1.2 Analysis

Several non-compendial analytical methods for the determination of pentosan polysulfate sodium in pharmaceutical formulations were available. These included normal-phase high-performance liquid chromatography with refractive index detection, capillary electrophoresis with ultraviolet detection, surface plasmon resonance, and gel-permeation chromatography with refractive index detection. The analytical methods are summarized in [Table 1.1](#). No compendial analytical methods were available to the Working Group.

1.3 Production

1.3.1 Production process

As a semi-synthetic compound, the polysaccharide backbone of pentosan polysulfate sodium, xylan, is present in beech tree bark. Extracted xylan from beech bark or other plant sources is treated with sulfating agents (e.g. chlorosulfonic acid or sulfonyl chloride). After sulfation, pentosan polysulfate is treated with sodium hydroxide to form a sodium salt of the compound ([Deshpande et al., 2010](#)).

1.3.2 Use

(a) Indications

Orally administered pentosan polysulfate sodium is used primarily in the treatment of interstitial cystitis. It is one of only two products approved for treatment of this bladder condition and is often used after inadequate response

to the other, which is irrigation of the bladder with dimethyl sulfoxide ([Hanno et al., 2011](#)). With its large, heparin-like molecular structure, pentosan has anticoagulant and fibrinolytic properties ([MicroMedex, 2013](#)), although this use was not observed in recent data from the USA. Pentosan was approved by the Food and Drug Administration for the indication of “relief of bladder pain or discomfort associated with interstitial cystitis” ([FDA, 2013](#)). In the European Union, other formulations apart from the oral form include ointment, rectal suppository, and injectable solution. Pentosan is also used in veterinary medicine as an anti-inflammatory drug to treat arthritis ([MicroMedex, 2013](#)).

(b) Dosage

Pentosan polysulfate sodium can be administered orally, intramuscularly, rectally, or as a solution instilled into the bladder. For the treatment of interstitial cystitis, recommended dosing is an oral dose of 100 mg, three times per day, for at least 3 months ([IMS Health, 2012b](#)). Use for deep venous thrombosis prophylaxis involves intramuscular injection of 50 mg every 12 hours ([MicroMedex, 2013](#)).

(c) Trends in use

Pentosan polysulfate sodium is not widely used in the USA, with 138 000 drug uses reported in office-based physician visits in 2012 ([IMS Health, 2012b](#)). Use had declined by 33% since 2005 ([Fig. 1.1](#)). Based on NDTI data, approximately 50 000 patients in the USA were exposed to pentosan in 2012 ([IMS Health, 2012b](#)). About 450 000 prescriptions for pentosan were dispensed in the USA in 2012, down slightly from about 490 000 in 2008 ([IMS Health, 2012c](#)).

Despite an only modest volume of use, total worldwide sales of pentosan were nonetheless US\$ 276 million in 2012, with 82% occurring in the USA. The only other countries with appreciable use were Spain (US\$ 16 million) and Canada (US\$ 11 million) ([IMS Health, 2012a](#)).

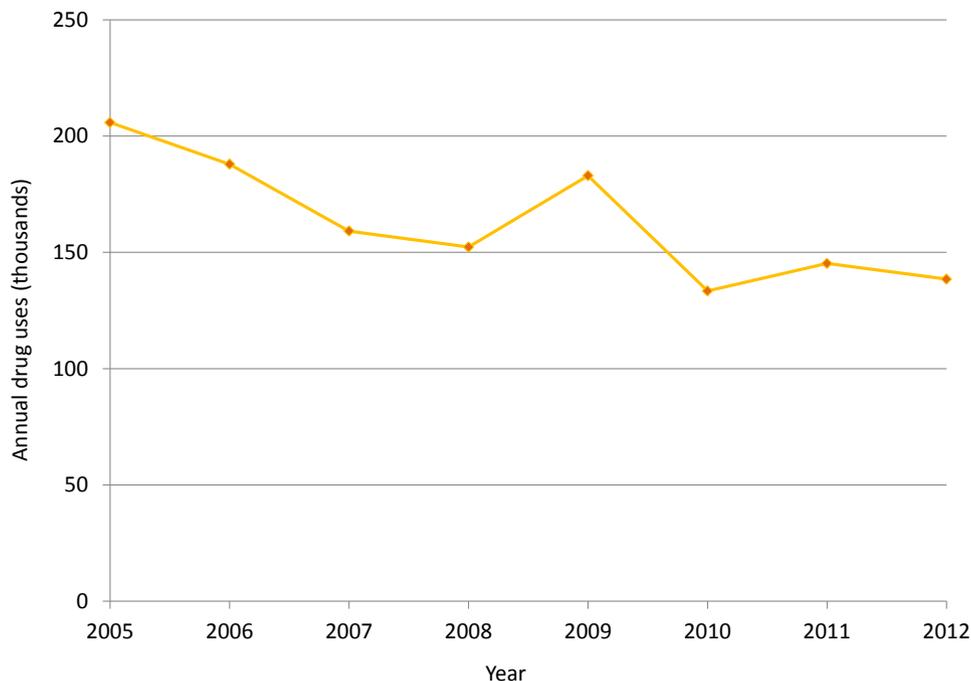
Table 1.1 Some non-compendial analytical methods for pentosan polysulfate sodium

Sample matrix	Sample preparation	Assay method	Detection limit	Reference
Human plasma	–	Immunoassay – indirect ELISA	2.6 ng/mL (LLOQ)	Abnova (2013)
Human serum	Blood collection in tubes containing oxalate, separation of plasma by centrifugation	Amplified ELISA using mAb 5-B-10 that recognizes 2,3-, 2,6-, and 4,6-disulfate ester ring substitution in pyranose-containing polysaccharides	50 ng/mL (LOD)	Kongtawelert & Ghosh (1990)
Human urine	Urine sample, centrifugation, incubation with equal volume CPC citrate buffer, centrifugation, dissolve precipitate in lithium chloride, addition of ethanol to mixture, centrifugation, dry precipitate with nitrogen, addition of 0.5 M HCl, hydrolysis, dry sample in vacuum oven, derivatization with TMS reagent	GC-FID Glass column Detector: FID Carrier gas: nitrogen, 30 mL/min	10 µg/mL (LOD)	Lee et al. (1986)
Rabbit serum	Collection of blood from rabbit ear, separation of serum by centrifugation	Antiviral bioassay method based on inhibitory activity of PPS on HIV-2 virus in MT-4 cells (human T-lymphoblastoid cell line). Infection of MT-4 cells with HIV-1 or HIV-2 in culture medium, transfer to microtitre tray wells containing serum samples, 5-day incubation at 37 °C, number of viable cells by MTT	0.5 µg/mL (LOD)	Witvrouw et al. (1990)
Nanoparticles	Drop-wise addition of a solution of standard PPS to solution of chitosan, magnetic stirring, separation by centrifugation	CZE Buffer: Tris base in water (50–200 mM) pH 3.0–6.5 Pressure: 10–35 mbar Running voltage: –10 or 10 to –30 or 30 kV based on separation mode (normal or reversed) Injection time: 5–10 s	0.1 mg/mL (LOQ)	Abdel-Haq & Bossù (2012)
Formulation	–	HPLC Column: silica diol Mobile phase: sodium chloride (200 mM) Flow rate: 1 mL/min Detector: refractive index		Muller et al. (1984)
Formulation	Dilution of 10 mg of PPS with 10 mL of purified water	CZE using indirect detection Fused silica capillary Detector: UV detector (217 nm) Applied voltage: –20 kV (capillary inlet at cathode) Current: 14.4 µA Running buffer: BTC buffer, 8.75 mmol/L		Degenhardt et al. (1998)

Table 1.1 (continued)

Sample matrix	Sample preparation	Assay method	Detection limit	Reference
Formulation	Dilution of 10 mg PPS with 10 mL purified water	Reverse polarity CZE using a central composite design CE-UV diode-array detector Polyimide coated fused silica capillary Detector: 320 nm (reference wavelength: 217 nm) Running buffer: BTC buffer, 8.75 mmol/L	0.25 mg/mL (LOQ)	Prochazka et al. (2003)
Formulation	–	SPR technology, biosensor analysis with immobilized enzymes HNE, HAase or lysozyme Immobilization of enzymes: amine coupling Binding assays in HEPES-containing buffer Flow rate: 50 µL/min Regeneration: 100 mM acetic acid containing 2.0 M sodium chloride	0.3 µg/mL (LOQ)	Shen et al. (2003)
Formulation	Dilution in deionized water	HPLC methods (1) Column: diol GPC Mobile phase: 25 mM potassium phosphate, monobasic; 25 mM potassium phosphate, dibasic; 50 mM potassium chloride Flow rate: 0.7 mL/min Detector: refractive index (2) Column: diol GPC Mobile phase: acetonitrile in water (5 : 95); 25 mM potassium phosphate, monobasic; 25 mM potassium phosphate, dibasic; 50 mM potassium chloride Flow rate: 0.7 mL/min Detector: refractive index (3) Column: diol GPC Mobile phase: 0.9% sodium chloride in water Flow rate: 0.5 mL/min Detector: refractive index		NTP (2004)

BTC, benzene-1,2,4-tricarboxylic acid; CE, capillary electrophoresis; CPC, cetyl pyridinium chloride; CZE, capillary zone electrophoresis; ELISA, enzyme-linked immunosorbent assay; ELISA, enzyme-linked immunosorbent inhibition assay; FID, flame ionization detector; GC, gas chromatography; GPC, gel permeation chromatography; HAase, hyaluronidase; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HIV, human immunodeficiency virus; HNE, human neutrophil elastase; HPLC, high-performance liquid chromatography; LOD, limit of detection; LLOQ, lower limit of quantitation; LOQ, limit of quantitation; MAb, monoclonal antibody; min, minute; MTT, 3'-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; PBS, phosphate buffered saline; PPS, pentosan polysulfate sodium; SPR, surface plasmon resonance; TMB, 3,3',5,5'-tetramethylbenzidine; TMS, trimethylsilyl; UV, ultraviolet

Fig. 1.1 Reported use of pentosan by office-based physicians in the USA

Prepared by the Working Group based on data obtained from [IMS Health \(2012b\)](#)

1.4 Occurrence and exposure

Pentosan polysulfate sodium does not occur in nature. Human exposure is largely limited to use as a medication. While occupational exposure in manufacturing is likely to occur, no specific studies on occupational or environmental exposure to pentosan were identified by the Working Group.

1.5 Regulations and guidelines

Pentosan has been approved by drug regulatory agencies primarily in the European Union and USA. In the USA, it was approved by the Food and Drug Administration in 1996 ([FDA, 2013](#)). The Working Group did not identify extraordinary regulatory restrictions on the use of pentosan as a medication, or regulations on environmental exposure.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Mouse

See [Table 3.1](#)

In one study of oral administration, groups of 50 male and 50 female B6C3F₁ mice (age, 6 weeks) were given pentosan polysulfate sodium (pharmaceutical grade) at doses of 0 (control), 56, 168, or 504 mg/kg body weight (bw) in deionized water by gavage once per day on 5 days per week for 104 to 105 weeks. A significant decrease in body weight was seen in females at the highest dose, but not in males or any other groups of females. Survival of all dosed groups was similar to that of controls. Liver haemangiosarcomas

Table 3.1 Studies of carcinogenicity in mice given pentosan polysulfate sodium by gavage

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence,(%) and/or multiplicity of tumours	Significance	Comments
Abdo et al. (2003), NTP (2004) B6C3F ₁ (M, F) 104–105 wk	Administered at doses of 0, 56, 168, or 504 mg/kg bw in deionized water, 5 days per week, for 104–105 wk 50 M and 50 F/group	<i>Males</i> Liver haemangiosarcoma: 2/50*, 0/50, 4/50, 9/50** Hepatocellular adenoma: 19/50, 15/50, 15/50, 20/50 Hepatocellular carcinoma: 11/50, 13/50, 15/50, 13/50 Hepatocellular adenoma or carcinoma (combined): 23/50***, 23/50, 26/50, 31/50** <i>Female</i> Liver haemangiosarcoma ^a : 1/50, 1/49, 1/50, 4/49 Hepatocellular adenoma: 7/50****, 5/49, 4/50, 15/49** Hepatocellular carcinoma: 3/50, 3/50, 5/50, 3/50 Hepatocellular adenoma or carcinoma (combined): 10/50 ^a , 8/49, 9/50, 18/49 Malignant lymphoma: 7/50 [#] , 8/50, 6/50, 16/50**	*P < 0.001 (Poly-3 trend test) **P ≤ 0.05 (Poly-3 test) ***P = 0.031 (Poly-3 trend test) ****P = 0.003 (Poly-3 trend test) ^a P = 0.010 (Poly-3 trend test) [#] P = 0.006 (Poly-3 trend test)	Purity, pharmaceutical grade

^a Incidence in historical controls receiving NTP-2000 diet in 2-year studies: 24/959 (2.6% ± 1.4%); range, 0–4% bw, body weight; F, female; M, male; wk, week

occurred with a positive trend in males, with the incidence at the highest dose significantly increased compared with controls. The incidence of liver haemangiosarcoma in females at the highest dose (4 out of 49; 8%) exceeded the incidence of this tumour in historical controls (24 out of 959, 2.6%; range, 0–4%). There was a significant increase in the incidence of malignant lymphoma in females at the highest dose.

The incidences of hepatocellular adenoma or carcinoma (combined) increased with positive trends in males and in females. The incidences of hepatocellular adenoma in females at the highest dose, and of hepatocellular adenoma or carcinoma (combined) in males at the highest dose were also significantly increased. The incidences of hepatocellular adenoma in treated males, and of hepatocellular carcinoma in treated males or treated females, were not significantly increased ([Abdo et al., 2003](#); [NTP, 2004](#)).

3.2 Rat

See [Table 3.2](#)

In one study of oral administration, groups of 50 male F344/N rats (age, 6 weeks) received pentosan polysulfate sodium (pharmaceutical grade) at oral doses of 0 (control), 14, 42, or 126 mg/kg bw, and groups of 50 female F344/N rats (age, 6 weeks) received pentosan polysulfate sodium at oral doses of 0 (control), 28, 84, or 252 mg/kg bw by gavage in deionized water, once per day, 5 days per week, for 104–105 weeks. There was no effect on body weight or survival in any of the groups of treated rats during the study. There were no significant increases in the incidence of any neoplasm in treated rats ([Abdo et al., 2003](#); [NTP, 2004](#)).

Table 3.2 Studies of carcinogenicity in rats given pentosan polysulfate sodium by gavage

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence, (%) and/or multiplicity of tumours	Significance	Comments
Abdo et al. (2003) , NTP (2004) F344/N (M, F) 104–105 wk	Male rats were given doses of 0, 14, 42, or 126 mg/kg bw, and female rats were given doses of 0, 28, 84 or 252 mg/kg bw by gavage in deionized water, 5 days per week, for 104–105 wk 50 M and 50 F/group	See comments		Purity, pharmaceutical grade There were no significant increases in the incidence of any neoplasm

bw, body weight; F, female; M, male; wk, week

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

[Fellstrom et al. \(1987\)](#) measured pentosan polysulfate sodium in plasma and in urine by radioassay after intravenous and oral administration in a group of eight healthy volunteers. After intravenous administration of 40 mg of pentosan, plasma clearance was 49.9 ± 6.6 mL/minute, of which renal clearance constituted 4.2 ± 1.2 mL/minute. Only 8% of the intravenous dose was recovered in the urine, suggesting that there was extensive metabolism. After daily oral dosing with 400 mg of pentosan, steady-state trough plasma concentrations were low (20–50 ng/mL), and bioavailability was 0.5–1%.

The oral bioavailability of pentosan was investigated in 18 healthy young male volunteers who received pentosan as an intravenous dose of 50 mg, or an oral dose of 1500 mg, or a placebo ([Faaij et al., 1999](#)). Intravenously administered pentosan significantly increased activated partial thromboplastin time and the activity of anti-factor Xa, hepatic triglyceride lipase, and lipoprotein lipase compared with placebo in a magnitude comparable to other heparin-like

compounds administered intravenously. Orally administered pentosan did not influence any of the parameters compared with placebo.

[MacGregor et al. \(1984\)](#) studied the catabolism of pentosan polysulfate sodium. Five healthy male volunteers were given [125 I]-labelled pentosan in conjunction with unlabelled pentosan at a dose of 0.1, 1, 7, or 50 mg intravenously. The half-lives for doses of 0.1–7 mg ranged from 13 to 18 minutes. At a dose of 50 mg, the half-life was 45 minutes. Tissue distribution studies showed that most of the radiolabelled material was localized in the liver and spleen. Pentosan was desulfated in the liver and spleen and depolymerized in the kidney, and it is likely that desulfation and depolymerization of pentosan is saturable.

[Simon et al. \(2005\)](#) studied two groups of eight healthy fasted female volunteers who sequentially received a single oral dose of 200 μ Ci of [3 H]-labelled pentosan supplemented with 300 mg of unlabelled pentosan, or 300 μ Ci of [3 H]-labelled pentosan supplemented with 450 mg of unlabelled pentosan. Most (84%) of the administered oral dose was excreted in the faeces as intact pentosan, and a smaller percentage (6%) was excreted in the urine as pentosan of low relative molecular mass and desulfated pentosan.

Excretion of pentosan was studied in 34 female patients with interstitial cystitis who were receiving long-term treatment with pentosan ([Erickson et al., 2006](#)). The median concentration of pentosan in the urine of these patients

was 1.2 µg/mL (range, 0.5–27.7 µg/mL). All the pentosan recovered from the urine of these patients was of low relative molecular mass.

4.1.2 Experimental systems

In a pharmacokinetic study of pentosan in New Zealand rabbits, [¹²⁵I]-labelled pentosan as marker was injected simultaneously with increasing doses of unlabelled pentosan (Cadroy *et al.*, 1987). The data indicated that prolongation of the half-life of pentosan with increasing doses resulted from progressive reduction in the clearance of the drug, with a constant volume of distribution.

Some studies of distribution were oriented towards the pharmacological application of pentosan in the treatment of interstitial cystitis. Kyker *et al.* (2005) used fluorescently labelled chondroitin sulfate to track the distribution of glycosaminoglycans administered intravesically to C57BL/6NHsd mouse bladder that had been damaged on the surface. Bladder damaged by trypsin or hydrochloric acid bound the labelled chondroitin sulfate extensively on the surface, with little penetration into the bladder muscle.

In rabbits given 1–1.2 mg of pentosan by intravenous administration, median recovery in the urine was 47.2% (range, 19.7–73.2%) for unfractionated pentosan, 74.6% (range, 31.4–96.3%) for pentosan of low relative molecular mass, and 3.3% (range, 2.5–5.0%) for pentosan of high relative molecular mass. In rabbits given 1.0–1.2 mg pentosan by oral administration, median recovery in the urine was 7.45% (range, 2.1–46.0%) for pentosan of low relative molecular mass, and 0.1% (range, 0.0–0.3%) for pentosan of high relative molecular mass (Erickson *et al.*, 2006).

Sprague-Dawley rats were given [³H]-labelled pentosan orally or intravenously at a dose of 5 mg/kg bw, and killed 1 or 4 hours later, respectively. Autoradiography indicated extensive distribution of radiolabel in the whole animal

after intravenous administration, with notable labelling of connective tissues, and low activity in bone and cartilage. There was a high concentration of radiolabel in the urine, and preferential localization of radiolabel to the lining of the urinary tract. After oral administration, the tissue distribution of radiolabel was similar, but activity was lower (Odland *et al.*, 1987).

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

(a) Mutagenicity

Pentosan polysulfate sodium was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535, with or without metabolic activation, at a concentration range of 100 to 10 000 µg/plate (NTP, 2004).

(b) Chromosomal damage

No consistent increase in the frequency of micronucleated polychromatic erythrocytes was seen in bone-marrow cells of male F344/N rats or male B6C3F₁ mice given pentosan at doses of 156.25–2500 mg/kg bw by gavage, three times at 24-hour intervals. An initial trial had yielded a weakly positive result (*P* for trend = 0.019) in male rats, but a second trial gave clearly negative results (NTP, 2004). A subsequent study in male and female B6C3F₁ mice given pentosan as a daily dose at 63, 125, 250, 500, or 1000 mg/kg bw by gavage for 3 months also gave negative results. There were no significant differences in the percentages of polychromatic erythrocytes in the circulating blood of mice receiving pentosan (NTP, 2004).

4.3 Other mechanistic data relevant to carcinogenicity

4.3.1 Effects on cellular physiology

Pentosan polysulfate sodium can antagonize the binding of fibroblast growth factor-2 (FGF-2) to its cell surface receptors, and has been shown to modulate the angiogenic activity of FGF-2 in tumours in humans and mice. [Jerebtsova et al. \(2007\)](#) studied the role of FGF-2 and pentosan in the pathogenesis of intestinal bleeding in mice. The results indicated that high steady-state levels of circulating FGF-2, plus anticoagulant activity, are needed to induce lethal intestinal bleeding in mice.

Treatment with pentosan prevents the progression of nephropathy in streptozotocin-induced diabetes in ageing C57B6 mice by decreasing albuminuria, renal macrophage infiltration, and expression of tumour necrosis factor- α ([Wu et al., 2011](#)).

[Zugmaier et al. \(1992\)](#) concluded that pentosan is an in-vitro inhibitor of a variety of heparin-binding growth factors released from tumour cells. Of seven tumour cell lines tested, six (breast cancer: MDA-MB-231, MDA-MB-435, MDA-MB-468; lung cancer: A-549; prostate cancer: DU-145; and epidermoid carcinoma: A-431) were resistant to pentosan in soft-agar cloning assays, and did not appear to depend on autocrine stimulation by the heparin-binding growth factors. In contrast to this resistance in vitro, subcutaneous growth of tumours from all cell lines in athymic nude mice was inhibited in a dose-dependent fashion by daily intraperitoneal injections of pentosan.

Pentosan inhibits virus adsorption to cells in vitro as demonstrated by monitoring the association of radiolabelled HIV-1 virions with MT-4 cells ([Baba et al., 1988](#)).

4.3.2 Effects on cell proliferation

[Elliot et al. \(2003\)](#) observed that pentosan has marked effects on the growth and extracellular matrix of smooth-muscle cells cultured from human prostate. Pentosan decreased cell proliferation and extracellular-matrix production. This suggested that the drug may have therapeutic potential in relation to benign prostatic hyperplasia.

The results of treatment of three prostate-cancer cell lines (LnCaP, PC3, and DU145) with pentosan have been reported ([Zaslau et al., 2006](#)). In LnCaP cells, there was a mean inhibition of growth of $12\% \pm 7\%$ at 24 hours ($P = 0.025$), and $20\% \pm 15\%$ at 72 hours ($P < 0.001$). Similar inhibition was observed in the other two cell lines.

[Rha et al. \(1997\)](#) reported that growth of gastric-cancer cell lines expressing midkine, a novel heparin-binding growth/differentiation factor, was inhibited by pentosan, which was described as a heparin-binding blocking agent.

[Zaslau et al. \(2004\)](#) reported that pentosan significantly inhibited the growth of ZR75-1 breast-cancer cells; however, a significant increase in cell proliferation ($25\% \pm 2\%$; $P < 0.001$) was observed in estrogen-independent MCF-7 breast-cancer cells.

The effects of pentosan on tumour growth, hyperprolactinaemia and angiogenesis in diethylstilbestrol-induced anterior pituitary adenoma in F344 rats was described by [Mucha et al. \(2002\)](#). Long-term treatment with pentosan did not cause any changes in pituitary weight, serum prolactin concentration, or density of microvessels. However, there was an increase in the number of apoptotic bodies within the anterior pituitary.

The mechanism of cell motility inhibition by pentosan appears to be independent of cytoskeletal structural alterations, including changes in microfilament and microtubule networks ([Pienta et al., 1992](#)). In vitro, pentosan altered

cellular contacts with the extracellular matrix and inhibited cell motility. In vivo, pentosan prolonged survival of male rats injected with highly metastatic cells.

4.4 Susceptibility

No data were available to the Working Group.

4.5 Mechanistic considerations

Most of the experimental studies on pentosan polysulfate sodium were not directed towards elucidating a possible mechanism of carcinogenesis. No mechanism of carcinogenesis was indicated by the collective findings.

5. Summary of Data Reported

5.1 Exposure data

Pentosan polysulfate sodium is a drug of high relative molecular mass that is obtained by chemically treating the bark of the beech tree. It is used in oral form to treat bladder conditions (interstitial cystitis) and in injectable form for the prevention of blood clots. A large proportion of the global use of pentosan occurs in the USA (global sales in 2012, US\$ 276 million, with 82% occurring in the USA), where prescriptions have been declining over the past years.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Pentosan polysulfate sodium was tested for carcinogenicity in one study in male and female mice treated by gavage, and in one study in male and female rats treated by gavage.

In mice, pentosan caused a significant increase in the incidence of liver haemangiosarcoma in males at the highest dose, and an increase in the incidence of liver haemangiosarcoma that occurred with a positive trend in males. The incidence of liver haemangiosarcoma in females at the highest dose exceeded the incidence in historical controls. It caused a significant increase in the incidence of malignant lymphoma in females at the highest dose. Exposure to pentosan increased the trend in the incidences of hepatocellular adenoma or carcinoma (combined) in males and females and also caused a significant increase in the incidence of hepatocellular adenoma in females and hepatocellular adenoma or carcinoma (combined) in males at the highest dose.

In treated rats, there were no significant increases in the incidence of any neoplasm.

5.4 Mechanistic and other relevant data

In humans, pentosan polysulfate sodium is desulfated in the liver and spleen and depolymerized in the kidney. Intravenous administration of radiolabelled pentosan to rats indicated extensive distribution of radiolabel, particularly in connective tissues, a high concentration of radiolabel in the urine, and a preferential localization of radiolabel to the lining of the urinary tract.

Pentosan was not mutagenic when tested in *Salmonella typhimurium*, with or without metabolic activation. Likewise, no evidence of chromosomal damage associated with exposure to pentosan was obtained in studies in rodents.

In vitro, pentosan is an inhibitor of a variety of heparin-binding growth factors released from tumour cells.

The data did not support any genotoxic mechanism of carcinogenesis by pentosan.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of pentosan polysulfate sodium.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of pentosan polysulfate sodium.

6.3 Overall evaluation

Pentosan polysulfate sodium is *possibly carcinogenic* to humans (Group 2B).

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