# Chinese expert consensus on the use of oral propranolol for treatment of infantile hemangiomas (version 2022)

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**Abstract:** Infantile hemangioma (IH) is the most common benign vascular neoplasm in children. Although the probability of spontaneous regression is very high, large and rapidly growing hemangioma may result in various sequela after spontaneous involution. Therefore, except for hemangiomas that grow in concealed sites, are small in size, or are in a stable state that can undergo "watchful waiting", aggressive treatment is often required. Since 2008, propranolol has gradually replaced glucocorticoids and become recognized worldwide as first-line treatment for IH. Many studies have reported on its treatment mechanism, both domestically and internationally, resulting in expert consensus and clinical practice guidelines. In recent years, with the continuous accumulation of clinical experience and growing number of studies, there has been a deepening understanding of the pathogenesis of hemangiomas and mechanism of action of propranolol. Thus, it is necessary to update the expert consensus to be more consistent with clinical practice in order to guide medication management and provide scientific norms for the clinical use of propranolol in the treatment of IH. This updated version simplifies the clinical examination, medication, and monitoring process for the use of propranolol in the treatment of IH, making it easier to use.

**Keywords:** Propranolol; infantile hemangioma (IH); expert consensus

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Infantile hemangioma (IH), also referred to as hemangioma, is the most common benign vascular neoplasm in children, with an incidence of about 4–10% (2) and even higher in premature babies and low-birth weight infants (3). The ratio of male to female cases of IH is about 1:3–5. IHs mainly occur in the head, neck, trunk, and limbs (4), and about 67% are solitary, 4% multiple, and 13% regional. The typical clinical manifestation is a growth cycle involving a proliferative phase, involuting phase, and involuted phase.

Although the probability of spontaneous regression is very high (60–90%), large and rapidly growing hemangiomas may leave pigmentation, vascular dilatation, fibrofatty tissue redundancy, and scarring after regression, and in about 10% of cases, ulceration, bleeding, infection, and pain, resulting in disfiguration and affecting quality of life. Hemangiomas located at certain sites may cause organ dysfunction (such as loss of visual axis), limited joint motion, dyspnea, and other serious complications, some even life-threatening. In addition, especially when the lesion occurs on the head and neck, huge social and psychological pressure is also exerted on patients during the growth and development period and on their parents. Therefore, except for hemangiomas that grow in concealed sites, are small in size, or are in a stable state that can undergo "watchful waiting", aggressive treatment is required. The earlier the treatment, the better the cosmetic results and functional recovery (5).

The treatment of IH should be based on the patient's age, the phase and type (superficial, deep, or compound) of hemangioma, as well as the sites and severity of the lesions. The ultimate goal is to obtain the best therapeutic effect with minimal comprise and economic cost. There are 3 main treatment methods, namely drug therapy (oral administration, topical use, or intratumoral injection), surgical treatment, and laser treatment, with priority given to drug therapy.

Previously, glucocorticoids were used as first-line treatment of hemangiomas (6). Since Léauté-Labrèze *et al.* (7) first reported in 2008 that propranolol had a distinct effect on hemangiomas, its efficacy and safety have been evaluated in a large number of clinical studies. Currently, propranolol has replaced glucocorticoids and is recognized as the first-line treatment for IH. The United States (8) and Europe (9) have issued expert consensus or recommendations on the treatment of IH with propranolol. Hemangeol® R oral solution (propranolol hydrochloride), a pediatric drug from Pierre Fabre Dermatologie (France), was approved by the United States Food and Drug Administration for marketing on March 14, 2014, becoming the first drug specifically used for the treatment of proliferative IH. The first domestic drug for the treatment of IH, "Hemeijia" (propranolol hydrochloride oral solution), was approved by the National Medical Products Administration (NMPA) for marketing on June 25, 2021, which was promising news for the majority of infants with IH.

Since 2009, propranolol has been increasingly used in the treatment of IH in China (10), achieving the same good effect as that found in other countries. In addition, numerous studies on the mechanism of action of propranolol in the treatment of IH have been conducted. In order to standardize the application of propranolol in the treatment of IH, avoid overtreatment or undertreatment, and reduce the occurrence of complications, a Chinese expert consensus on the treatment of IH with propranolol was formulated and issued in 2016 after joint discussion by many well-known domestic experts from different specialties engaged in the diagnosis and treatment of IH (11). In 2019, after extensive discussions, pediatric surgery specialists also developed an expert consensus in their field of expertise (12). However, with the continuous accumulation of clinical experience and growing number of studies, there has been a deepening understanding of the pathogenesis of hemangioma and mechanism of action of propranolol. Thus, it is necessary to update the expert consensus to be more consistent with clinical practice in order to guide medication management and provide scientific norms for the clinical use of propranolol in the treatment of IH. This updated version simplifies the clinical examination, medication, and monitoring process for the use of propranolol in the treatment of IH, making it easier to use.

## Pharmacological mechanism of propranolol in the treatment of IH

Propranolol is a synthetic, nonselective beta-adrenoceptor blocker that can block both beta 1 and beta 2 receptors, causing a decrease in heart rate and blood pressure. The chemical term for propranolol is 1-isopropylamino-3-(1-naphthyloxy)-2-propanol hydrochloride, the molecular formula is $C_{16}H_{21}NO_2 \cdot HCl$, and molecular weight is 295.81. The exact mechanism of propranolol in the treatment of IH is still unclear (13). It is generally believed that the early effect of propranolol is a reduction in nitric oxide release to cause vasoconstriction (within 1–3 days after initiation), the interim effect is the inhibition of angiogenesis by blocking proangiogenic signals, and the long-term effect is achieved by inducing endothelial cell apoptosis (*Figure 1*).

Propranolol blocks beta adrenoceptors without producing alpha antagonism, eliminating epinephrine-mediated vasodilation, resulting in a net effect of vasoconstriction. Blockade of beta 2 receptors by propranolol can inhibit the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-nitric oxide signaling pathway (14,15), leading to constriction of blood-supplying capillaries in hemangiomas, reduction of blood flow in hemangiomas, and slowing of

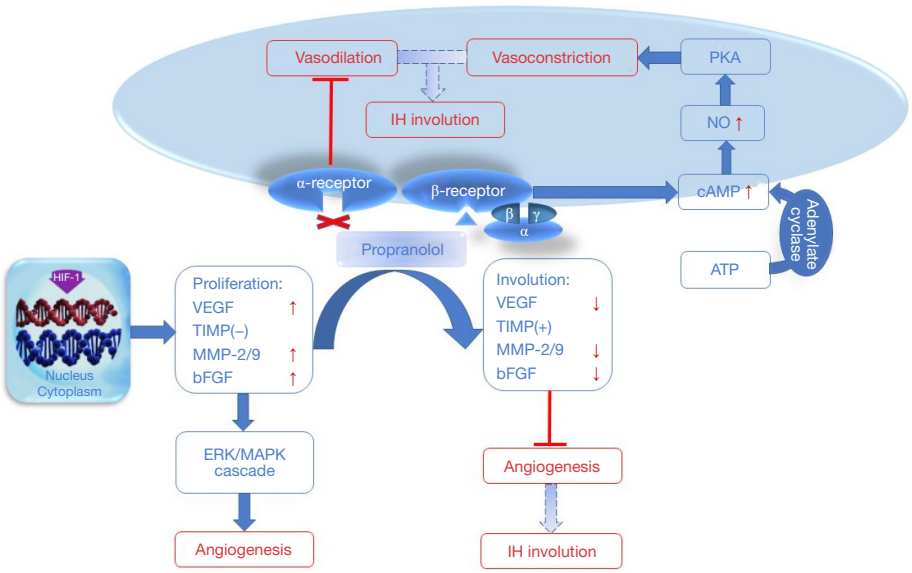


**Figure 1** Molecular mechanism of propranolol in the treatment of hemangiomas. HIF, hypoxia-inducible factor-1; IH, infantile hemangioma; PKA, protein kinase A; NO, nitric oxide; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; VEGF, vascular endothelial growth factor; TIMP, tissue inhibitor of metalloproteinases; MMP, matrix metalloproteinase; bFGF, basic fibroblast growth factor; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase.

IH growth, resulting in significant changes and palpable softening of cutaneous hemangiomas within 1–3 days after the initiation of propranolol treatment.

A previous study (14) showed that the expression of proangiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were increased in various cells in IH, including vascular endothelial cells, pericytes, and connective tissue cells. In proliferative IHs, the level of serum VEGF increased; in contrast, the expression of VEGF and bFGF was significantly decreased in involuting and involuted hemangiomas. However, tissue inhibitor of metalloproteinases (TIMP) was only expressed in involuting hemangiomas (16). Propranolol can result in decreased expression of hypoxia-inducible factor 1α (HIF-1α), VEGF, matrix metalloproteinase-2 (MMP-2), and MMP-9 in proliferative hemangiomas, thereby inhibiting angiogenesis by reducing endothelial cell growth and migration (14,17). Epinephrine and norepinephrine can induce the expression of VEGF and proteases (e.g., MMP-2 and MMP-9) required for extracellular matrix remodeling (14), and HIF-1α/VEGF/MMPs lead to activation of the proangiogenic cascade [extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) cascade], thereby promoting angiogenesis.

The rate of cell apoptosis is low in proliferative hemangiomas but increases approximately 5 times in involuting hemangiomas, which is associated with decreased expression of a family of B cell lymphoma 2 (bcl-2) proteins that inhibit apoptosis (14). Propranolol induces apoptosis in many types of cells, including endothelial cells in vitro, possibly by blocking beta 2 receptors (18). Thus, induction of apoptosis may be an additional mechanism through which propranolol treats IH.

## Indications

Propranolol is indicated for the treatment of proliferative IH that requires systemic treatment and for a small number of children with involuting IH (19).

(I) Possible obstruction of organs: eyes, ears, airways, and anoperineal area.

(II) Large hemangioma with the risk of causing high output cardiac failure.

(III) IHs with ulceration are prone to occur (intertriginous sites): cervical folds, axilla, and anoperineal area.

(IV) Sites at risk of permanent deformity or functional impairment: periorbital area, nose, lip, female breast area, liver, and spinal cord.

## Contraindications

### *Relative contraindications*

(I) Frequent asthma.
(II) Abnormal blood pressure and heart rate and sick sinus syndrome.
(III) Endocrine system diseases such as pheochromocytoma.
(IV) Drug interactions: the following drugs should be carefully selected or prohibited when used simultaneously: calcium channel blockers, other antihypertensive drugs, antiarrhythmic drugs (such as propafenone, quinidine, amiodarone, and lidocaine), digitalis drugs, nonsteroidal anti-inflammatory drugs, lipid-lowering drugs, rifampicin, and phenobarbital (20).

### *Absolute contraindications*

(I) Recent or ongoing episodes of hypoglycemia.
(II) Second-degree or third-degree atrioventricular block.
(III) Allergy to propranolol or any of its other ingredients (20).

## Premedication examination

For patients determined to receive propranolol, a detailed medical history, physical examination, and auxiliary examinations are required to exclude arrhythmia, severe cardiac block, congenital heart disease, tracheitis, pneumonia, and asthma. Routine blood work, coagulation test, anteroposterior chest X-ray, thyroxine level, blood glucose level, myocardial enzyme level, liver function, renal function, and electrolyte determination are not listed as routine examinations.

### *Medical history inquiry*

The medical history inquiry includes whether premature or not, weight at birth, maternal medication history during pregnancy (especially progesterone), maternal past medical history (connective tissue disease), feeding condition, with or without family history of respiratory system disease and cardiovascular system disease, with or without history of birth trauma, and critical first aid after birth (21).

### *Physical examination*

Physical examinations include nutritional status examination, heart and lung auscultation, and special examination for IH.

### *Other examinations*

An electrocardiogram (ECG) is required for any of the following circumstances. (I) Low heart rate: less than 120 beats/minute in newborns (<1 month), below 100 beats/minute in infants (1–12 months), and below 90 beats/minutes in children aged 1–3 years. (II) A family history of congenital heart disease or arrhythmia (such as conduction block, long Q-T interval, sudden death), or mother with connective tissue disease. (III) Child with a history of arrhythmia or abnormal heart rate found on auscultation (10).

Children at risk of hypoglycemia (premature, low birth weight, growth retardation, newborns, malnutrition, or a history of hypoglycemia) need to have their blood glucose levels tested.

Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) of the brain should be performed in children with multiple IHs of the face and neck before starting treatment. For children with suspected PHACES (posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies) syndrome, ECG and echocardiography should be performed prior to starting medication, and the examination results should be evaluated jointly by pediatric, ophthalmology, and otorhinolaryngology experts. For children with multiple systemic hemangiomas (≥5 lesions), systematic screening is required to exclude whether they have hemangiomas of internal organs, the most common being liver hemangiomas (12).

## Method of administration

At present, there is no unified opinion on the age of earliest administration of propranolol. It is generally recommended for infants aged >2 weeks old or premature babies with corrected age of ≥2 weeks. The standard dose is 2 mg/kg/day.

For full-term infants aged >4 weeks without severe complications, with normal birth weight, and normal diet and weight gain, the drug can be administered on an outpatient basis, without requiring dose escalation. The initial dose is 2 mg/kg/day, taken orally in 2 divided doses at an interval of more than 8 hours, with or after meals. Subsequently, patients are asked to present to hospital every 1–2 months, and the dose is adjusted according to body weight and response to the drug (22).

Children with severe lesions (including children with

PHACE syndrome), corrected age less than 5 weeks, body weight <2.5 kg, a risk of hypoglycemia, poor general condition (complicated with cardiovascular or respiratory disease), lesions located around the airway, nose, and other important organs, and presenting with symptoms such as dyspnea should be hospitalized for observation for 3–7 days and given a small dose under close monitoring, with an initial dose of 0.5 mg/kg/day taken orally in 2–3 doses. Resting heart rate, blood pressure, or blood glucose are measured before the first dose and then repeated every 30–60 minutes for 2–4 hours. If there is no obvious adverse reaction, the dose is gradually increased after 1 week until obvious effects appear, the maximum dose is not more than 2 mg/kg/day, and the minimum interval for dose increase is 24 hours.

Propranolol oral solution is 120 mL, comprising 450 mg (as propranolol), equivalent to 3.75 mg of propranolol in 1 mL (20), from which milliliters per dose can be calculated. While medicating, the solution should be taken strictly according to the doctor's instructions. Unless serious complications or other systemic diseases appear, the dose should not be reduced or stopped without permission to avoid rebound growth.

It has been reported that a small number of children (incidence of less than about 1%) are resistant to propranolol, i.e., the tumors continue to grow or do not shrink in size after oral administration of propranolol at 2 mg/kg/day for at least 4 weeks (23). In such cases, prednisone may be added at 1 mg/kg once every other day after eating in the morning (24). The patients' medication regimen should be revisited once a month to determine whether it should be continued or adjusted as appropriate.

## Post-medication monitoring

For outpatient drug users, parents or guardians are asked to observe changes in complexion, respiration, heart rate, and temperature of extremities after each drug administration. If any problems are found, they should be managed promptly. Routine blood pressure measurements are not required. For hospitalized patients, medication should be performed under ECG monitoring, and changes in essential vital signs such as blood pressure, heart rate, respiration, and blood glucose should be closely monitored. If serious adverse reactions occur, timely treatment should be given. If the following problems are present, the dosage should be reduced or the drug temporarily discontinued until heart rate and blood pressure return to a safe range. (I) Bradycardia: below 120 beats/minute in newborns (<1 month), below 100 beats/minutes in infants (1–12 months), and below 90 beats/minute in children aged 1–3 years; (II) Hypotension (systolic blood pressure): <57 mmHg in newborns, <85 mmHg in infants aged 6 months, and <88 mmHg in children aged 1 year (25).

In case of hyperpyrexia (>38.5 ℃), cough or severe upper respiratory tract infection, pneumonia, asthma, or diarrhea during the medication period, the drug should be temporarily discontinued for observation and re-administrated after recovery. In case of other special circumstances, timely return to the doctor is necessary.

### *Response after treatment*

The response rate of propranolol to proliferative hemangiomas is more than 90%. One week after medication, hemangiomas begin to become paler, shrunken, and soft. Three months after medication, most hemangiomas are shrunken remarkably. By about 1 year of age, most hemangiomas have resolved, leaving telangiectasia or fibrofatty tissue redundancy. Redundancy changes are more common in the first 8 weeks after administration and at the age of 5–6 months (11).

### *Duration*

The effect of propranolol on proliferative IH is most pronounced during the first week, followed by a slow improvement and sometimes a plateau. Drug therapy generally needs to last for 6–12 months, and earlier drug withdrawal will lead to rebound growth of the hemangiomas.

### *Drug discontinuation criteria*

When hemangiomas are completely involuted, or the patients' age is over 1 year (26), or the hemangiomas have progressed to the involuting phase, drug discontinuation is considered. The majority of pediatric patients can safely discontinue the drug at the age of 12–14 months.

### *Drug discontinuation*

Tapered drug withdrawal is recommended, i.e., the medication frequency is halved in the first 2 weeks after the decision to withdrawal, the dose is halved in the second 2 weeks, and the drug is discontinued in week 5 (27). If

rebound growth is found during or after drug withdrawal, the drug should be continued for 1 month or longer according to the original regimen until the hemangioma is completely resolved, or the drug is discontinued if there is no change in size for more than 2 months.

If propranolol is abruptly withdrawn after its use for more than 2 weeks, cardiac hypersensitivity may occur within 24–48 hours. This is known as propranolol withdrawal syndrome, which stems from abrupt withdrawal of propranolol, after which cardiac β-adrenergic sensitivity increases, resulting in increased blood pressure and heart rate, which peaks within 4–8 days and gradually diminishes after 2 weeks (28).

Although propranolol is effective in most IHs, rebound growth after drug withdrawal is not uncommon, with an incidence of 19–25% (29). Influencing factors include duration of medication for less than 9 months, female sex, location in the head and neck, segmental distribution, and deep involvement.

### *Follow-up management*

Patients with hemangiomas completely involuted but with telangiectasias left in the skin can be managed with laser therapy, and those with red pigmental change can be treated with topical β-receptor blockers (such as propranolol ointment, timolol cream, timolol eye drops, etc.) (30) or laser irradiation. Sclerotherapy or elective surgery can be selected for those with residual fibrofatty tissue mass or obvious protrusion.

## Adverse reactions and prevention

The incidence of adverse reactions to propranolol in the treatment of IH is low. Generally, adverse reactions are mild in severity and do not require special treatment. Serious adverse reactions may occur in a small number of patients and should be given sufficient attention. Common adverse reactions (>10%) include gastrointestinal reactions (diarrhea, abdominal pain, constipation in a few children, and severe vomiting in some children), sleep disorders (dysphoria or somnolence), respiratory symptoms (bronchospasm, asthma attack, or infection), hypotension, and cold limbs. The proportion of adverse reactions requiring treatment to cease does not exceed 2%. Adverse reactions with an incidence of <1% include hypoglycemia, decreased heart rate (bradycardia), urticaria, alopecia, and changes in myocardial enzymes. Adverse reactions can occur as soon as 20 minutes after administration (31), and hypotension can occur 2 hours after administration, returning to normal 3 hours later (32). The effects of propranolol on growth and development and the nervous system of pediatric patients need to be further investigated.

### *Hypoglycemia*

Propranolol can cause hypoglycemia in children, especially when taking the medicine without regular meals or with vomiting. Manifestations of hypoglycemia include spasms, somnolence, or coma. Once any of the symptoms occur, the drug should be discontinued immediately and emergency treatment should be carried out. In addition, the risk of hypoglycemia is easily increased in the case of coadministration with corticosteroids. To reduce the risk of hypoglycemia, administration must be performed with or after meals.

### *Bradycardia and hypotension*

Propranolol may cause or worsen bradycardia or hypotension with a mean decrease in heart rate of 7 beats/minute. In case of severe (<80 beats/minutes) or symptomatic bradycardia, or severe hypotension (systolic blood pressure <50 mmHg), the drug should be discontinued.

### *Bronchospasm*

Propranolol may cause bronchospasm and is contraindicated in patients with a history of asthma or bronchospasm. If a lower respiratory tract infection associated with dyspnea and gasping occurs during the treatment period, the drug should be suspended.

### *Neurological and psychiatric symptoms*

In clinical trials, adverse reactions such as somnolence, sleep disorders, nightmares, anxiety, and irritability were commonly reported with the use of propranolol hydrochloride oral solution but usually did not require treatment.

### *Others*

Hyperkalemia has been reported in large, ulcerated infantile hemangiomas. Electrolyte monitoring should be

performed in such patients. Blood pressure is decreased by propranolol, which may increase the risk of stroke in patients with PHACE syndrome with cerebrovascular malformations. Patients with large facial hemangiomas need to be diagnosed for underlying arteriopathy associated with PHACE syndrome before treatment with propranolol.

Beta receptor blockers may interact with anesthetics, leading to attenuation of reflex tachycardia and increased risk of hypotension. It is necessary to inform the anesthesiologist that the patient is being treated with beta receptor blockers. If the use of general anesthesia is planned, the beta receptor blockers should be discontinued at least 48 hours earlier (20).

In order to avoid potential risks, prior to administration, parents or guardians should be provided with written information on treatment and adverse effects of propranolol as well as contact details in case of emergency. They should be told to deliver the drug at least 8 hours apart, with or after meals, and temporarily suspend the drug in case of insufficient oral intake, gastroenteritis, or respiratory tract infection. Vaccination can be implemented normally during the period of administration. For patients with allergy susceptibility, it is recommended the drug be discontinued 1–2 days before vaccination. A few children have experienced mild liver dysfunction (elevated transaminase and alkaline phosphatase) during medication, but it is unclear whether this was directly related to use of propranolol. If necessary, the medication can be suspended and liver-protecting drugs can be used to promote recovery.

## Use and concomitant medication of other beta receptor blockers

When propranolol is contraindicated or ineffective, or intolerable side effects occur in the patient, other beta receptor blockers such as atenolol (33,34) and nadolol (35) may be considered. These options appear to be comparable to or even better than propranolol in terms of efficacy and safety. Atenolol is a selective beta 1 receptor antagonist and therefore has a low risk of bronchospasm and hypoglycemia. The drug is administered at 1 mg/kg/day in the treatment of IH, but for children with heart problems, the prescribed dose can be up to 2 mg/kg/day. Nadolol is a nonselective beta receptor antagonist, has no intrinsic sympathomimetic activity, and has little inhibitory effect on the myocardium. However, once absorbed, nadolol is not metabolized and is excreted primarily unchanged in the feces. Any case that affects or slows gastrointestinal motility will favor its reabsorption and accumulation. In addition, a study in mice (36) showed that propranolol, atenolol, and nadolol, regardless of their ability to cross the blood-brain barrier, induced the release of nitric oxide and nitrogen peroxide from the hypothalamus, which might have deleterious neurologic side effects. Further studies are needed, with particular attention to the pharmacokinetic processes of these drugs in infants and young children.

For compound IH and thick superficial IH, oral propranolol alone may have a slower effect and take longer. However, when combined with topical beta receptor blockers, the treatment time may be significantly shortened and regression of the hemangioma may be accelerated, particularly for large and periorbital hemangioma, for which the effect is more obvious, and complications are reduced (37,38). At present, 0.5% timolol maleate eye drops (off-label prescription use) is the most commonly used clinical topical preparation, which can be administered to the affected area by wet compress or mixed with medicated dressing gel for application. Timolol maleate is a nonselective and potent beta receptor antagonist which can block both beta 1 and beta 2 receptors, and its effect is 8 times that of propranolol. Timolol maleate has been shown to have good effect when used topically on its own for the treatment of superficial hemangioma (39). Currently, a timolol maleate gel for hemangioma is under clinical trial. The dosage of propranolol can be reduced when in combination with topical timolol maleate, which can ensure efficacy and also reduce potential adverse effects.

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## Footnote

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of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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