

An extensive safety database of more than 85 studies on Reb A and other components of the stevia plant support Reb A's use in tabletop sweeteners, beverages and cereals. Steviol glycosides including Reb A have been reviewed by several authoritative bodies, including the FAO/WHO Joint Expert Committee on Food Additives (JECFA) and Foods Standards Australia New Zealand (FSANZ) and in 2008 two panels of internationally recognized experts concluded that Reb A meets the Generally Recognized as Safe (GRAS) criteria established by the Food and Drug Administration (FDA). The following table summarizes the body of research on steviol glycosides and Reb A.

Conclusions	Support Points	References
<p>Reb A is a safe natural sweetener for all consumers, including those with diabetes.</p>	<p>More than 85 studies have evaluated the metabolism and safety of Reb A and its related steviol glycosides.</p> <p>Peer-reviewed studies addressed absorption, distribution, metabolism, pharmacokinetics and excretion. Acute, subchronic, chronic and developmental studies in animals and studies in humans confirm the safety of Reb A.</p>	<ul style="list-style-type: none"> <li>• JECFA, 2008</li> <li>• FSANZ, 2007</li> <li>• GRAS No. 252</li> <li>• GRAS No. 253</li> </ul>
<p>The highest estimated intake of Reb A is no more than 5 mg/kg body weight/day, which is well below the Acceptable Daily Intake (ADI) of 12 mg/kg bw/day. At this ADI a 150 pound person could safely consume 30 packets of PureVia daily.</p>	<p>Intake estimates for Reb A, as used to sweeten beverages, cereals, cereal bars and as a tabletop sweetener, illustrated that typical sweetener users could consume approximately 2 mg Reb A/kg bw/day, while the consumers with large intakes of these foods (the 90<sup>th</sup> percentile) could consume approximately 5 mg Reb A/kg bw/day.</p>	<ul style="list-style-type: none"> <li>• GRAS No. 252</li> </ul>
<p>Reb A and its related glycosides share the same metabolic pathway, thus the safety data for understanding any steviol glycoside is relevant to understanding the safety of Reb A.</p>	<p>After it is consumed, Reb A travels to the intestine without being changed or absorbed. While in the intestine, glucose molecules are removed from Reb A. Then Reb A is excreted in the feces or absorbed and transported to the liver where it is conjugated to a carbohydrate and excreted in either the feces or urine.</p>	<ul style="list-style-type: none"> <li>• JECFA, 2008</li> <li>• FSANZ, 2007</li> <li>• GRAS No. 252</li> <li>• GRAS No. 253</li> </ul>
<p>Independent scientists and medical experts have reviewed the database of more than 85 studies of the safety of steviol glycosides, including Reb A, and have confirmed Reb A meets the FDA's criteria for being Generally Recognized as Safe (GRAS).</p>	<p>Research shows no acute, subchronic, chronic or developmental toxicity even at the highest doses tested. In addition, it shows no genotoxicity at intake levels below 8000 mg/kg bw/day, which is well below the estimated daily intake. Research also shows no effects on blood glucose levels. Blood pressure is not affected in individuals with normal blood pressure and only slightly reduced in people with untreated hypertension.</p>	<ul style="list-style-type: none"> <li>• JECFA, 2008,</li> <li>• FSANZ, 2007</li> <li>• GRAS No. 252</li> <li>• GRAS No. 253</li> </ul>

**Table 2: Additional information about the metabolism of Reb A**

<b>Metabolism Topic</b>	<b>Conclusions</b>	<b>Support Points</b>	<b>References</b>
Absorption of Reb A and other steviol glycosides from the GI tract	Only steviol can be absorbed into the body – the rate of its absorption is determined by the number of glucose molecules.	<p>Before stevioside or Reb A can be absorbed, glucose molecules must be removed by bacteria in the gut.</p> <p>After all glucose molecules have been removed, the remaining compound is steviol.</p>	<ul style="list-style-type: none"> <li>• Geuns, et al., 2003a</li> <li>• Wingard et al., 1980</li> <li>• Nakayama et al., 1986</li> <li>• Hutapea et al., 1997</li> <li>• Koyama et al., 2003a,b</li> <li>• Geuns and Pietta, 2004</li> <li>• Roberts and Renwick, 2008</li> <li>• Renwick and Tarka, 2008</li> </ul>
Conjugation to facilitate elimination and excretion	Steviol is not stored in the body.	Steviol is bound to a carbohydrate called a glucuronide, which is eliminated in feces or urine.	<ul style="list-style-type: none"> <li>• Geuns et al., 2003a</li> <li>• Koyoma et al., 2003b</li> <li>• Gardana et al., 2003</li> <li>• Geuns et al. 2007</li> <li>• Nakayama et al., 1986</li> <li>• Simonetti et al., 2004</li> <li>• Roberts and Renwick, 2008</li> <li>• Wheeler et al 2008</li> </ul>

**Table 3: Additional information from the data on safety**

<b>Safety Info.</b>	<b>Conclusions</b>	<b>Support Points</b>	<b>References</b>
Acute toxicity	Research shows no adverse effects for Reb A, even at extremely large doses.	Animal studies delivering up to 15,000 mg/kg bw/day show no adverse effect.	<ul style="list-style-type: none"> <li>• Toskulkao et al., 1997, as cited in JECFA, 1999</li> <li>• Medon et al., 1982</li> </ul>
Subchronic toxicity	Research shows no adverse effects for Reb A, even at the highest doses tested.	<p>Studies have found no systemic toxicity for Reb A, even when the highest doses (4000 mg/kg bw/day) were tested over a 90-day period.</p> <p>Some studies report decreased weight gain, however this is not considered to be an adverse effect.</p>	<ul style="list-style-type: none"> <li>• Nikiforov and Eapen, 2008</li> <li>• Curry and Roberts, 2008</li> </ul>
Chronic toxicity/ Carcinogenicity	Stevioside does not cause cancer.	Rat studies conducted up to 2 years in duration found no evidence of carcinogenicity for stevioside. No observable adverse effects were detected at levels equivalent to 1.2% and 5% of the diet, which is equivalent to 600 or 970 mg/kg/bw/day.	<ul style="list-style-type: none"> <li>• Xili et al., 1992</li> <li>• Toyoda et al., 1997</li> </ul>
Developmental/ Reproductive toxicity	Reb A and stevioside are not reproductive toxicants in multi-generational studies in animals.	<p>Results from several two generation reproduction studies on Reb A and stevioside found no developmental effects.</p> <p>The no observable adverse effect level (NOAEL) was 2000 mg/kg bw/day.</p>	<ul style="list-style-type: none"> <li>• Curry et al., 2008</li> <li>• Yodyingyuad and Bunyawong, 1991</li> <li>• Mori et al., 1981</li> <li>• Takanaoka et al., 1991, as cited in JECFA, 1999</li> <li>• Usami et al., 1995</li> <li>• Wasuntarawat et al., 1998</li> </ul>

Safety Info.	Conclusions	Support Points	References
Genotoxicity	The World Health Organization's (WHO) Joint Expert Committee on Food Additives (JECFA) concluded that there would be no genotoxic effects at doses up to 8000 mg/kg bw/day.	A full array of genotoxicity studies have been conducted including standard <i>in vitro</i> and <i>in vivo</i> studies. <i>In vivo</i> studies confirm that no genotoxicity occur from Reb A as a sweetener.	<ul style="list-style-type: none"> <li>• Matsui et al., 1989,1996a</li> <li>• Klongpanichpak et al., 1997</li> <li>• Suttajit et al., 1993</li> <li>• Pezzuto et al., 1985a,b,1986</li> <li>• Terai et al., 2002</li> <li>• Compadre et al., 1988</li> <li>• Procinska et al., 1991</li> <li>• Oh et al., 1999</li> <li>• Temcharoen et al., 2000</li> </ul>
<b>Special Studies</b>			
Blood pressure – animal studies	Some animal studies of stevioside show blood pressure is reduced.	Several studies on potential changes in blood pressure have been conducted; most report a reduction in blood pressure.	<ul style="list-style-type: none"> <li>• Dyrskog et al., 2005a,b</li> <li>• Jeppesen et al., 2003</li> <li>• Liu et al., 2003</li> </ul>
Blood pressure – human studies	Blood pressure is not affected in individuals with normal blood pressure and only slightly reduced in people with untreated hypertension.	Research on blood pressure changes in normal and diabetic individuals consuming steviol glycosides or Reb A have found no significant reductions. Previous studies found some decrease among people with untreated hypertension who consumed stevioside for 1 or 2 years.	<ul style="list-style-type: none"> <li>• Gregersen et al., 2004</li> <li>• Chan et al., 2000</li> <li>• Hsieh et al., 2003</li> <li>• Jeppesen et al., 2006</li> <li>• Geuns et al., 2007</li> <li>• Barriocanal et al., 2008</li> <li>• Jeppesen et al., 2006</li> <li>• Maki et al, 2008a,b</li> <li>• FSANZ, 2007</li> </ul>
Blood glucose – animal studies	Reb A does not affect markers for blood glucose control.	Multiple studies on normal rats, mice and diabetic rats have investigated Reb A and stevioside for effects on blood glucose, insulin and glucagon. No effects have been reported in any of the studies at doses up to 2000 mg/kg bw/day.	<ul style="list-style-type: none"> <li>• Lailerd et al., 2004</li> <li>• Suanarunsawat and Chaiyabutr, 1997</li> <li>• Jeppesen et al., 2002</li> <li>• Xili et al., 1992</li> <li>• Nikiforov and Eapen, 2008</li> </ul>

Safety Info.	Conclusions	Support Points	References
Blood glucose – human studies	Reb A can be consumed by people with diabetes.	Human studies providing 5 mg/day to 1500 mg/day of Reb A or stevioside for 1 day to 2 years have found no changes in blood glucose or insulin.	<ul style="list-style-type: none"> <li>• Geuns et al., 2007</li> <li>• Curi et al., 1986</li> <li>• Barriocanal et al., 2008</li> <li>• Maki, et al., 2008b</li> <li>• Haebisch, 1992</li> <li>• Geuns et al., 2007</li> <li>• Ferri et al., 2006</li> <li>• Chan et al., 2000</li> <li>• Hsieh et al., 2003</li> <li>• Jeppesen et al., 2006</li> </ul>