that removal of specific amino acids from the media could also promote survival.[39] The interaction of yeast TOR with a CR diet was later examined more extensively in the context of yeast replicative lifespan. Deletion of either *TOR1* or the S6K1 homologue *SCH9* significantly extends yeast lifespan,[40] but CR is unable to further extend the lifespan of these mutants.[41]

A major advantage of studying aging in yeast, worms, and flies is the relative ease of conducting genetic screens for organisms with altered longevity. A number of experiments conducted in these organisms suggest that decreased or altered translation underlies the beneficial effects of both mTOR inhibition and CR on lifespan. One such study in yeast demonstrated that a reduced level of 60S ribosomal subunits significantly extends lifespan and is epistatic with CR.[42] Reduction of either ribosomal subunits or translation initiation factors significantly extends the lifespan of *C. elegans*, and the lifespan of CR worms is not further extended by inhibition of mTOR.[43] However, rapamycin treatment can extend the lifespan of flies on a CR diet, suggesting that although there may be significant overlap between CR and mTOR inhibition, there may also be additional mechanisms unique to each regimen.[44] Subsequent studies that compared mice placed on either CR or rapamycin have identified both overlapping and unique changes in the liver and white adipose transcriptome and the liver metabolome, supporting a model in which the effects of CR and mTOR inhibition do not completely overlap.[45–47]

14.3 Rapamycin Extends the Lifespan and Healthspan of Mice

In mammals, a seminal study conducted by the National Institute on Aging Interventions Testing Program in 2009 demonstrated that treatment with rapamycin could significantly extend the lifespan of genetically heterogeneous mice of both sexes.[48] Since that time, there have been at least 9 additional published studies demonstrating that rapamycin can extend the lifespan of wild-type inbred and outbred strains, conducted by many laboratories and using a variety of dosing regimens (Table 14.1).[49] Rapamycin shows efficacy at extending median as well as maximum lifespan in both sexes, even when begun late in life. Numerous studies in disease models have also been performed, also typically (but not always) resulting in a significant increase in lifespan (Table 14.2).

One concern about rapamycin has been the possibility that its effects on longevity may result from an anticancer effect rather than an effect on aging itself.[50] While rapamycin robustly extends the lifespan of genetically heterogeneous mice, which should avoid any confounding effects of rapamycin on lifespan resulting from an effect against strain-specific pathologies, a susceptibility to cancer is broadly shared by inbred mice. In comparison to calorie restriction (CR), which dramatically improves many different age-related phenotypes, rapamycin has modest results.[50,51]